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Hydrogen Cyanide Chemistry. 6. [1]Cyanogen Condensation with Cyanide, $C_7N_7^-$

D. W. Wiley,* O. W. Webster, and E. P. Blanchard

Contribution No. 1962 from the Central Research and Development Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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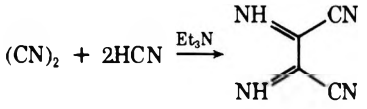
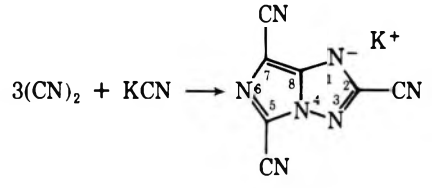
Three moles of cyanogen react with cyanide ion to give the salt of 1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile ($C_7N_7^-$, **1**). This structure is confirmed by its chemistry.

In the base-catalyzed condensation of hydrogen cyanide with cyanogen, diiminosuccinonitrile is formed via the additions of cyanide ion across the nitrile groups.[2] In the absence



of a proton source, we have found that cyanide ion reacts with *3* mol of cyanogen to give a C_7N_7 anion. For example, cyanogen reacts with an acetonitrile slurry of potassium cyanide to give KC_7N_7. This material, isolated as the dioxane solvate in 65% yield, is the potassium salt of 1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile[3] (**1**).



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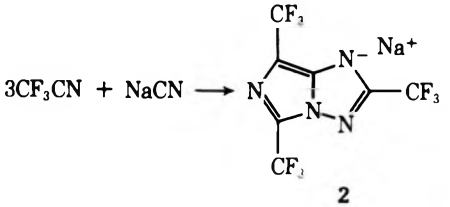
Trifluoroacetonitrile, another activated nitrile, undergoes the same type of cyclization reaction to give the corresponding tris(trifluoromethyl) compound **2**.[4] The structure of **2** was in



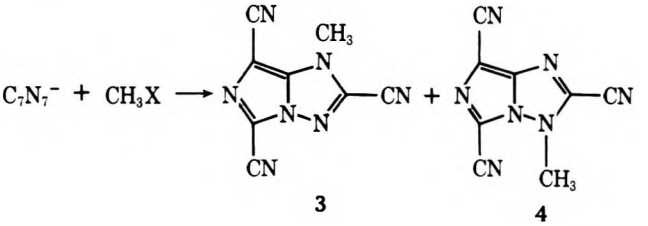
2

part based on the structure of **1**. This paper will describe work on which the structure of **1** is based.

The free acid from **1**, obtained either by treating the potassium salt with 9 N sulfuric acid or preferably by ion exchange, has a pK_a of −3 (extrapolated to water from spectrophotometric measurements in acetonitrile). Polarographic studies on $C_7N_7^-$ have shown an oxidation which is chemically but not electrochemically reversible. However, oxidation with chlorine yields only a chloro-C_7N_7 which reverts to C_7N_7H on contact with water.

The natural abundance ^{13}C NMR spectrum of KC_7N_7 in water shows seven peaks (87.8, 102.0, 110.7, 112.6, 114.9, 141.2, and 151.3 ppm downfield from Me_4Si) ruling out any symmetrical structure for **1**. The three peaks between 110 and 115 ppm (downfield from Me_4Si) occur in a range which has been reported for nitrile groups.[5]

KC_7N_7 can be alkylated to give a mixture of two isomers. Methylation gives the two isomers in a ratio of 1:3 with NMR peaks at δ 4.51 and 4.27, respectively, indicating *N*-methyl groups. Methylation can be carried out using a variety of methylating agents and solvents with not much change in the ratio of the isomers. The major isomer was shown to be the 1-methyl compound **3** by its ultimate conversion to 3-methylguanine **13** (see below) with the minor isomer being the

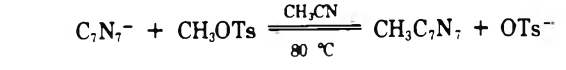


3 **4**

3-methyl compound **4**, supported by the presence of a $N_2CH_3^+$ ion in its mass spectrum.

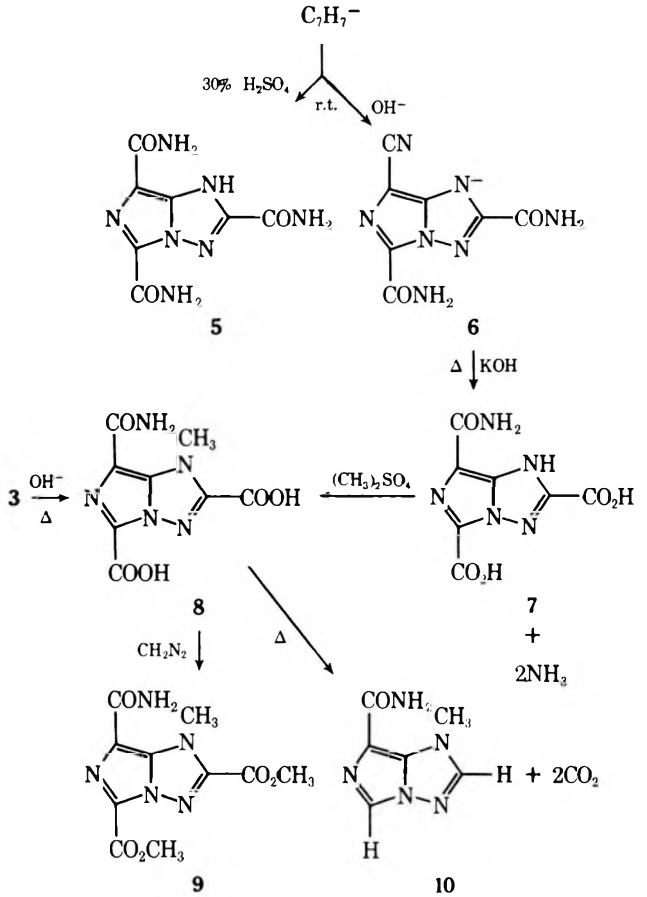
Methylation of the tris(trifluoromethyl) compound **2** gives a 1-methylated to 3-methylated product ratio of 93:7.[4]

Interestingly, methylation of $C_7N_7^-$ with methyl *p*-toluenesulfonate is an equilibrium reaction. The reverse reaction can be observed in the reaction of potassium *p*-toluenesulfonate with a pure single isomer of $CH_3C_7N_7$ to give $C_7N_7^-$ and the 1:3 mixture of methyl isomers.

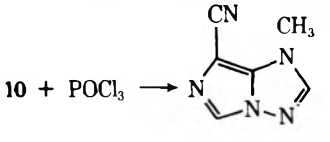


Hydrolysis of $C_7N_7^-$ in both acidic and basic media indicated three nitrile groups. With 30% sulfuric acid at room temperature, a base-soluble triamide (**5**) was formed in high yield. Other acidic conditions afforded mixtures. When $C_7N_7^-$ was allowed to stand for a few minutes at room temperature in 0.6 N hydroxide, the salt of a diamide nitrile **6**, $pK_a \simeq 4.5$, was quantitatively precipitated. Further basic hydrolysis at reflux (1.5 h) afforded 2 mol of ammonia and the tribasic amido dicarboxylic acid (**7**), pK_a = 0.93, 3.66, and 7.34.

Compound **7** was methylated at pH 10 to the methyl amido dicarboxylic acid (**8**), pK_a = 0.99 and 3.78, which was also obtained by base hydrolysis of the major $CH_3C_7N_7$ isomer **3**. Further methylation of **8** with diazomethane gave the trimethyl derivative **9** whose NMR spectrum showed 1 NCH_3 (δ 4.12) and 2 OCH_3 (δ 3.76). The presence of the two carboxylic acid groups was also substantiated by the ready decarboxylation of **8** to the *N*-methyl monoamide compound (**10**) whose NMR spectrum in D_2O showed two heterocyclic CH peaks at δ 8.17 and 7.79 and a NCH_3 at δ 4.00 along with a DOH peak indicating two exchanged hydrogens.



Conversion of the amide function in compound **10** with phosphorus oxychloride to a nitrile group, along with the two lost carboxylic groups, accounts for all three of the original nitrile groups. The NMR spectrum of the *N*-methyl nitrile compound **11** in deuterioacetone showed two heterocyclic CH's at δ 7.76 and 7.25 and the NCH_3 at δ 3.33. An attempt to dehydrate the amide group in **10** with acetic anhydride gave a monoacetyl compound which was hydrolyzed back to **10** in hot 2 N sodium carbonate. The solubility of the acetyl compound in cold base favors a structure with an acetylimide



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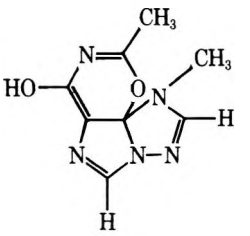

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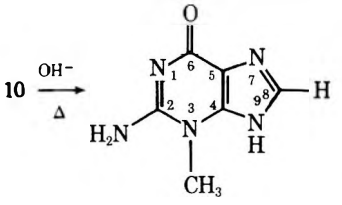
group but the shift in uv from 276 nm in **10** to 299 nm indicates the possibility of an *O*-acetyl derivative or the cyclized structure **12**.

The *N*-methyl monoamide **10** quantitatively isomerizes (30 min) in hot 0.5 N sodium hydroxide to 3-methylguanine **13**.[6] Assuming that there have been no rearrangements in the skeleton of $C_7N_7^-$, compound **10** has two of the original *C*-nitrile groups as CH with the other nitrile as an amide group. This leaves a nucleus of C_4N_4 with a methyl attached to one of the nitrogens. If the carbonyl of the amide group in **10** is the same as the carbonyl at carbon atom 6 in the 3-methylguanine, then a partial structure of **10** is **14**. Assuming minimum rearrangement in the isomerization, structure **15** is also possible for **10** where nitrogen atom c is connected to either carbon a. Structure **15** is eliminated, however, because $C_7N_7^-$ would be the symmetrical **16** which should have a ^{13}C NMR spectrum of five peaks at the most, with two peaks of relative intensity 2.



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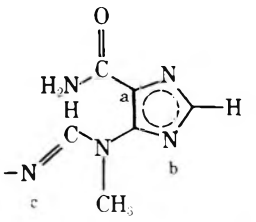

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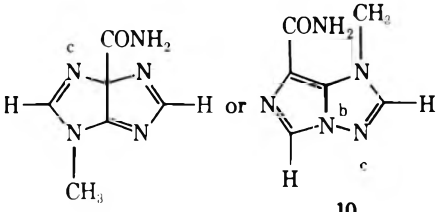

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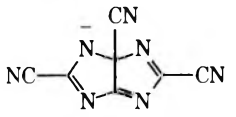
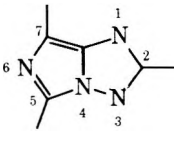


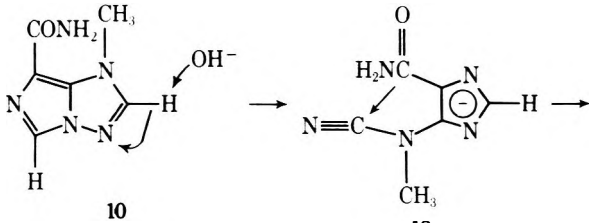
16

Therefore, barring any gross rearrangements in the degradations, $C_7N_7^-$ contains the heterocyclic nucleus 1*H*- or 3*H*-imidazo[1,5-*b*]-*s*-triazole (**17**) and KC_7N_7 is its 2,5,7-tricyano derivative.

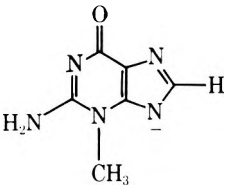


17

The rearrangement of **10** to 3-methylguanine is postulated to occur as follows:



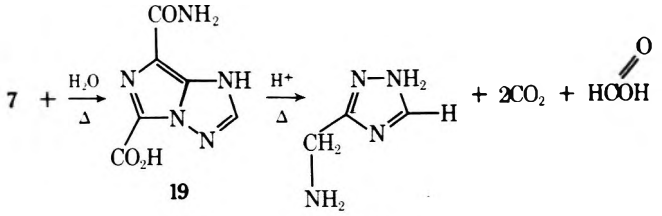
10 **18**



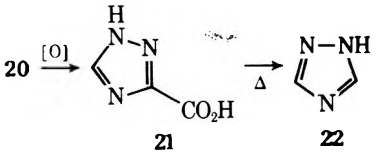
13

The attack of base on the triazole ring hydrogen gives the *N*-cyano intermediate, **18**, with the formation of the imidazole anion (further stabilized by resonance on the amide carbonyl) as the driving force.[7] This is followed by ring closure and tautomerization to 3-methylguanine.

The presence of the triazole ring is also shown by the acid hydrolysis and degradation of the tribasic amido dicarboxylic acid **7**. Refluxing its monopotassium salt in water (pH 5.60) gave 1 mol of carbon dioxide and the monodecarboxylation



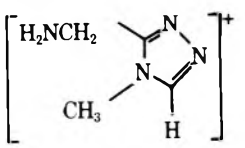
19 **20**



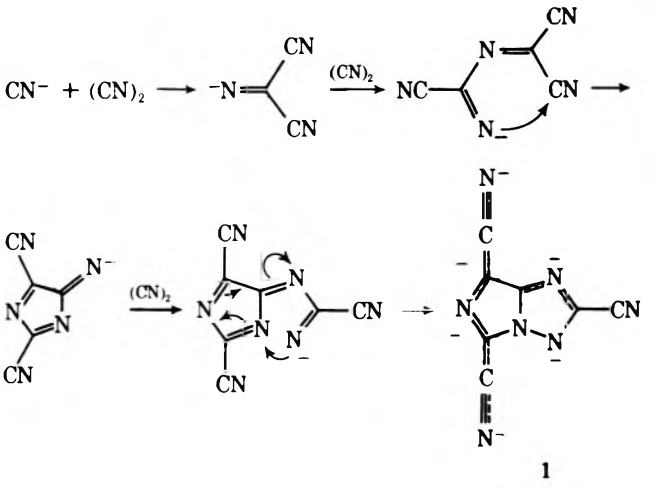
21 **22**

product **19**, which incidentally could be converted to the methyl amide **10** by methylation and decarboxylation. Prolonged treatment with more concentrated acid gave 3 mol of CO_2, 1 mol of formic acid, and 3-aminomethyl-1,2,4-triazole (**20**). Although 3-aminomethyl-1,2,4-triazole is described in the literature[8,9] (as the 2HCl and 2HBr salts), its structure was confirmed by oxidation to 1,2,4-triazole-3-carboxylic acid (**21**),[10] which was decarboxylated to 1,2,4-triazole (**22**).

The triazole ring was further noted in the very slow HCl hydrolysis of the methyl amide **10** to give a crude product characterized only by its lack of uv absorption and its mass spectrum which had a peak at *m/e* 112 as its highest mass peak of reasonable intensity. This corresponds to the fragment



The formation of KC_7N_7 with its structure defined by the chemical transformations described above must occur through the following reactions:



1

The anion is stabilized by having the negative charge delocalized over the ring system as well as two of the cyano groups.

Experimental Section

The mass spectral data were in general obtained using direct injection techniques and the intensities of the *m/e* peaks are grossly variable and only strong or pertinent peaks are listed. Detailed interpretations of the mass spectral data were hampered by the lack of related compounds, but empirical formulas assigned to *m/e* peaks are based on related deuterated isomers.

Potassium 1*H*-Imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile (1, KC_7N_7). A three-necked 1-l. flask equipped with a magnetic stirrer, thermometer, gas inlet tube, and dry ice condenser was flamed out under N_2. Anhydrous potassium cyanide (50 g, 0.8 mol, excess) and 500 ml of anhydrous acetonitrile were placed in the flask. The slurry was cooled under N_2 to 15 °C with a cold-water bath. Cyanogen gas (104 g, 2 mol) was then added over 50–90 min while maintaining the mildly exothermic reaction mixture between 20 and 25 °C. The resulting dark brown-red mixture was allowed to stir at 25 °C for an additional 1 h or until removal of the water bath caused no rise in temperature. The excess potassium cyanide was removed by filtration (washing with 50 ml of acetonitrile). The combined filtrates were carefully diluted with ca. 4 l. of ether to effect precipitation of a brown, water-sensitive, flocculent solid which was removed by filtration. The clear orange solution was concentrated under vacuum to give 135 g of **1** as an orange solid. Three recrystallizations from acetonitrile–dioxane (1:4 by volume) using Darco gave 110 g of colorless 1·2 dioxane. An additional 55 g of colorless product was obtained from the mother liquors for a total yield of 165 g (63%). The dioxane (44.3% by weight) was removed by drying at 140 °C (refluxing xylene) for 2 h under vacuum: uv (H_2O) max 313 nm (ε 16 600), 279 (11 300), and 220 (33 500), ir 2250 (m), 2220 (s), 2170 (w), 1560 (s), 1420 (m), 1380 (s), 1305 (s), 1290 (w), 1210 (s), 1185 (s), 997 (m), 740 (m), 715 (w), and 695 cm^{-1} (w). (Raman was not taken because of the fluorescence of $C_7N_7^-$ in the 430-nm range.)

The ^{13}C NMR spectrum of **1** in water was determined using a saturated solution (ca. 60%) of the dioxane-solvated salt in water. Using the dioxane as an internal standard, seven peaks were observed at 87.8, 102.0, 110.7, 112.6, 114.9, 141.2, and 151.3 ppm downfield from Me_4Si.

Anal. Calcd for C_7N_7K: C, 38.0; N, 44.3; K, 17.7; mol wt, 221. Found: C, 37.8, 37.9; N, 31.2, 37.0; K, 17.3; mol wt (by acetonitrile boiling point), 115–116 (indicating dissociation).

We could not obtain satisfactory nitrogen analyses on the anhydrous potassium salt presumably because of nitride formation. However, other salts described below obviated this problem.

This preparation has been run on two to three times this scale with yields varying from 45 to 65%. The 1·2 dioxane salt so obtained could be converted to the dihydrate by exposure to a stream of moist air. It was most convenient to store **1** as the dioxane salt since the dioxane (44% by weight) could easily be removed at 130 °C (refluxing xylene) under vacuum for 2 h, whereas the dihydrate was only difficultly dried (160 °C, 8 h or longer).

Other salts of $C_7N_7^-$ were prepared as described below. Aside from the sodium salt, they were prepared either by metathesis or by neutralizing the free acid HC_7N_7 (preparation below) with a carbonate or hydroxide of the desired metallic ion. An example of each procedure is illustrated. The others listed were prepared similarly and had satisfactory analyses.

Sodium C_7N_7. This was prepared from sodium cyanide and cyanogen in essentially the same manner as above at 25–29 °C. The crude reaction solution was passed through an alumina column (ethyl acetate eluent) to remove the bulk of the colored impurities. Recrystallization from dioxane–acetonitrile (2:1 by volume) gave the colorless salt, no mp <390 °C. A sample was analyzed as the hydrate (by alternate drying at 130 °C and exposing to moist air).

Anal. Calcd for $C_7N_7Na \cdot 2H_2O$: C, 34.9; H, 1.7; N, 40.7. Found: C, 34.8, 34.9; H, 1.9, 1.9; N, 40.7, 40.7.

Tetramethylammonium C_7N_7. A solution of 6.61 g (25.5 mmol) of 1 $2H_2O$ in 35 ml of water was treated with 5 g (excess) of tetramethylammonium chloride in 30 ml of water. The resulting precipitate was redissolved by heating the mixture to boiling. Cooling gave white, feathery needles, mp >300 °C, weighing 6.30 g (96%) after collecting, washing (25 ml of ice water), and air drying. It was recrystallized from water.

Anal. Calcd for $C_{11}H_{12}N_8$: C, 51.5; H, 4.7; N, 43.7. Found: C, 51.6; H, 4.7; N, 43.6.

Zinc $(C_7N_7)_2$. In an aqueous solution (60 ml) of 4.57 g (25 mmol) of HC_7N_7 (see below), zinc carbonate (1.57 g) was dissolved in small portions until the pH became 4. The slightly cloudy solution was filtered, treated with Darco (if necessary), and concentrated in vacuo at 80 °C to a dry foam which upon crushing and drying gave 4.3 g of free-flowing white powder.

Anal. Calcd for $C_{14}N_{14}Zn \cdot 1.5H_2O$: C, 36.8; H, 0.7; N, 43.0; Zn, 14.3. Found: C, 36.6; H, 0.4; N, 42.9; Zn, 14.2.

Lithium $C_7N_7 \cdot 2H_2O$: white powder, mp 320 °C dec.

Manganous $(C_7N_7)_2 \cdot 2C_2H_5OH$: yellow powder, darkening above 200 °C.

Cupric $(C_7N_7)_2 \cdot H_2O$: chocolate brown powder, darkening above 300 °C (water insoluble).

Silver C_7N_7: white needles from acetonitrile–water (water insoluble), no mp <300 °C.

Tetraethylammonium C_7N_7: white needles, mp 221–222 °C (7:1 H_2O–acetonitrile).

Trimethyloctadecylammonium C_7N_7: mp 118–119 °C (H_2O).

***N*-Methylphenazinium C_7N_7:** mixture of orange-yellow and deep red needles (3:1 H_2O–acetonitrile). Upon standing the orange needles turned red. Both forms behaved similarly upon heating, turned orange-red at 70–80 °C, and melted with decomposition at 159 °C.

Trimethylsulfonium C_7N_7: needles (2-propanol), mp 194–197 °C with bubbling to give mixture of methyl C_7N_7 isomers (see below).

Methyltriphenylphosphonium C_7N_7: white platelets, mp 152–153 °C (3:1 H_2O–ethanol).

1*H*-Imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile (HC_7N_7). A strong acid ion-exchange column was prepared by taking 100 ml of resin [Rexyn RG 50 (H), exchange capacity 1.9 mequiv/ml] and washing with water, 100 ml of 2 N HCl, and then water until pH 6. A solution of 1 $2H_2O$ [made from 39.7 g (0.1 mol) of KC_7N_7 2 dioxane by air drying overnight, weight loss 14 g] in 100 ml of water was passed through the column, collecting a total of 400 ml of solution washings. Concentration of the strongly acidic aqueous solution on a Rinco evaporator at 60 °C gave 19.0 g of crude HC_7N_7 as a red solid (theory 18.3 g). The uv spectrum of this material in water indicated it to be 96% pure.

An analytical sample was obtained by careful recrystallizations from anhydrous acetonitrile (1:5 w/v with 40% weight loss each time) to give almost white prisms, no melting point, turned dark brown by 200 °C and black at 250 °C. Recrystallization could also be effected from ethyl acetate–chloroform (35% weight loss) to give salmon-pink platelets: ir (KBr) 3225 (broad, m), 2260 (s), *1622* (*s*), 1505 (m), 1480 (m), 1450 (s), 1410 (m), 1332 (s), 1323 (sh, s), 1244 (w), 1227 (m), 1208 (s), 1185 (m), 1002 (m), 971 (w), 797 (m), 722 (w), 710 (m), 700 (m), and 657 cm^{-1} (s); uv (H_2O) same as I; (EtOH) max 325 nm (ϵ 13 000), 313 (17 300), 279 (11 700), and 229 (30 500); (CH_3CN) max 305 nm (ϵ 6900), 282 (5100), 262 (12 600), and 219 (27 000); NMR (Me_4Si internal) one sharp peak which shifted with solvent and traces of water, in CD_3COCD_3, δ 13.36; in CD_3SOCD_3, δ 10.28; and in CH_3CN, δ 8.98; MS *m/e* 183 (parent), with other strong peaks at *m/e* 131, 103, 79, 77, 53, and 38.

Anal. Calcd for C_7HN_7: C, 45.9; H, 0.6; N, 53.6; mol wt, 183. Found: C, 45.3; H, 0.9; N, 53.2, 53.6; neut equiv, 185.

Molecular weight, measured by vapor pressure osmometry in acetonitrile, was found to be 142, whereas by freezing point lowering in dimethyl sulfoxide, strong dissociation was noted in the values of 91 and 108, varying with concentration.

The pK_a was determined spectrophotometrically in acetonitrile, using tetraalkylammonium C_7N_7 salts.[11] Picric acid was used as hydrogen ion indicator as well as source of hydrogen ion. The pK_a values of HC_7N_7 in acetonitrile were 5.55 and 5.32. When converted to aqueous scale, using picric acid as conversion reference standard, the pK_i of HC_7N_7 is -3.1 ± 0.2. The validity of this conversion is based on the assumption that $C_7N_7^-$ behaves similarly to picrate ion in both acetonitrile and water.

Chlorination of 1. To a solution of 4.42 g (20 mmol) of KC_7N_7 in 35 ml of acetonitrile at 10 °C, 22 mmol of chlorine gas was added in a slow flow of N_2. The resulting colorless mixture was filtered to remove the bulk of the KCl. Concentration gave a very viscous oil which was then evaporatively distilled at 140 °C (0.1 mm). The colorless distillate of **1-chloro-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile** was resinous at room temperature and quite soluble in most organic solvents.

Anal. Calcd for C_7ClN_7: Cl, 16.3. Found: Cl, 16.2. 16.1.

The uv spectrum in dioxane showed a max of 285 nm (*k* varied markedly with concentration indicating strong π complexing). The addition of water caused the immediate appearance of those peaks characteristic of the $C_7N_7^-$ ion. The mass spectrum showed strong peaks (reported as ^{35}Cl peaks only) at *m/e* 217 ($C_7N_7Cl^+$), 189 ($C_7N_5Cl^+$), 182 ($C_7N_7^+$), *137* ($C_5N_3Cl^+$), 128 ($C_6N_4^+$), *102* ($C_5N_3^+$), 85 (C_3NCl^+), etc. It is the presence of the *m/e* 137 peak ($P - C_2N_4^+$) on which the 1-isomer structure is assigned.

Methylation of 1. A solution of 158.8 g (0.40 mol) of 1 2 dioxane in 1 l. of CH_3CN and 59.5 g (0.47 mol) of dimethyl sulfate was heated at reflux for 2 h with stirring. The solid, which deposited in the hot solution, was collected after cooling to 5 °C, thoroughly washed with 350 ml of CH_3CN, and dried under N_2 to give 54.1 g (90%) of methyl potassium sulfate. Concentration of the filtrate gave a gummy solid, which was washed with 250 ml of H_2O to give 77.0 g (97%) of a mixture of 1- and 3-methyl isomers, mp 180–198 °C. Four successive 100-ml extractions with tetrahydrofuran afforded 40.2 g of almost pure **1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile (3)**, mp 231–234 °C. An analytical sample, mp 234–235 °C, was obtained after three crystallizations from methyl ethyl ketone (MEK). Concentration of the tetrahydrofuran extracts, followed by fractional crystallization of the total mixture from MEK, afforded a total of 49.7 g of pure 1-methyl $C_7N_7^-$, mp 234.5–235 °C, in the head fractions: uv (EtOH) max 298 nm (ϵ 6600), 264 (12 500), and 221 (22 400); ir (KBr) 1630 cm^{-1}; NMR (CD_3COCD_3, Me_4Si internal) δ 4.27; MS *m/e* 197 (parent), other strong peaks at *m/e* 15 (CH_3^+), 38 (C_2N^+), 40 ($C_2H_2N^+$), 41 (CH_3CN^+), 52 ($C_2N_2^+$ and $C_3H_2N^+$), 64 ($C_3N_2^+$), 66 ($CH_2C_2N_2^+$), 67 ($CH_3C_2N_2^+$), 93 ($CH_3C_3N_3^+$), 102 ($C_5N_3^+$), 116 ($CH_2C_5N_3^+$), and 117 ($CH_3C_5N_3^+$). Empirical formulas were assigned from MS of $CD_3C_7N_7$ (1 isomer).

Anal. Calcd for $C_8H_3N_7$: C, 48.7; H, 1.5; N, 49.7. Found: C, 48.6, 48.7; H, 1.8, 1.7; N, 49.6, 49.8, 49.9.

Pure **3-methyl-3*H*-imdiazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile (4)**, mp 179.5–181 °C, was obtained from the tail fractions. An analytical sample, mp 182–183 °C (crystalline transition at 176 °C), was obtained by two recrystallizations from 1:1 chloroform–ethyl acetate (25 ml/g): uv (EtOH) max 336 nm (ϵ 20 900), 325 (16 600), 271 (3100), 248 (16 700), 240 (15 000), and 217 (22 100); ir (KBr) 1610 cm^{-1}; NMR (CD_3COCD_3, Me_4Si internal) δ 4.51; MS *m/e* 197 (parent), other strong peaks at *m/e* 15 (CH_3^+), 38 (C_2N^+), 43 ($CH_3N_2^+$), 52 ($C_2N_2^+$), 64 ($C_3N_2^+$), 66 ($C_3H_2N_2^+$), 93 ($C_4H_3N_3^+$), 102 ($C_5N_3^+$), and 145 ($CH_3C_5N_5^+$).

Anal. Found: C, 48.9, 48.7; H, 1.6, 1.7; N, 49.6, 49.7.

Analysis by NMR of the crude reaction product showed an isomer ratio of 3:1 for 1-:3-methyl isomers. Both isomers could be sublimed at 120–130 °C (0.1 mm), with no evidence (by NMR) for thermal interconversion at temperatures up to 230 °C. (The 3-methyl isomer slowly darkened in the melt at this temperature.) The same 3:1 ratio was noted when methylation was carried out with methyl iodide, methyl tosylate, trimethyloxonium fluoroborate, trimethylsulfonium iodide, and by reaction of diazomethane with HC_7N_7.

1-Methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarboxamide. To 10 ml of concentrated HCl was added 0.65 g of powdered **3** and the mixture was stirred for 36 h. After dilution with 10 ml of water, the solid was collected and washed with 95% ethanol and ether. The crude hydrolysate (0.90 g) was heated in dimethylformamide on a steam bath and filtered. After thorough drying, 0.63 g (79%) of the triamide was obtained as a microcrystalline solid, no mp <350 °C, ir no C≡N.

Anal. Calcd for $C_8H_9N_7O_3$: C, 38.2; H, 3.6; N, 30.1. Found: C, 38.6; H, 3.8, 3.5; N, 37.8, 38.1.

1-Benzyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile. A solution of 3.38 g of 1 and 10 ml of benzyl chloride in 25 ml of 1,2-dimethoxyethane was heated at reflux for 5 days. After cooling, 1.09 g of KCl was removed by filtration. Concentration of the filtrate gave a mixture of oil and solid which was slurried with ether. The resulting solid was collected and recrystallized to give 3.0 g of white needles, mp 149–152 °C.

Anal. Calcd for $C_{14}H_7N_7$: C, 61.5; H, 2.6; N, 35.9. Found: C, 61.2, 61.2; H, 2.6, 2.5; N, 35.2, 35.6.

1*H*-Imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarboxamide (5). To 25 ml of warm 30% (by weight, 20% by volume) H_2SO_4 was added 1.00 g of HC_7N_7. After standing overnight, the clear solution was diluted with 1 l. of H_2O to give **5** as a gelatinous precipitate. The solid was collected (very slow filtration) and washed extensively with H_2O. After air drying the white powder (electrostatic) weighed 1.23 g (95%). An analytical sample was dried at 80 °C for 12 h. The identical product was obtained using KC_7N_7 2 dioxane: uv (pH 13) max 335 nm (ϵ 20 600), 295 (8400), and 238 (24 400).

Anal. Calcd for $C_7H_7N_7O_3$: C, 35.4; H, 3.0; N, 41.3. Found: C, 35.5, 35.7; H, 2.9, 2.8; N, 41.6.

7-Cyano-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5-dicarboxamide (6). To 3.66 g (20 mmol) of HC_7N_7 in 7 ml of H_2O was added 60 ml of 1.000 N NaOH. The clear solution was stirred for 20 min and to the resulting slurry was added 40 ml of 1.000 N HCl. The pH was adjusted to 7 by adding 0.5 ml of saturated sodium bicarbonate. The entire mixture was heated to boiling and additional water was added to give a clear solution (total volume 350 ml). Cooling slowly to room temperature gave 3.51 g of the **sodium salt of 7-cyano-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5-dicarboxamide (6)** as fine needles, no mp <400 °C. An analytical sample was obtained by two recrystallizations from water. The free acid could be prepared by digestion in hot 30% acetic acid: uv (pH 12) max 323 nm (ϵ 17 700), 290 (8700), and 234 (29 600) with fluorescence at 491 nm (356-nm excitation); ir (KBr) 2230 (C≡N), and characteristic $CONH_2$ at 3160–3550 and 1695 cm^{-1}.

Anal. Calcd for $C_7H_4N_7O_2Na$: C, 34.9; H, 1.7; N, 40.7; Na, 9.5. Found: C, 34.4, 34.6; H, 2.1, 2.0; N, 40.4, 40.6; Na, 9.2.

7-Carboxamido-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5-dicarboxylic Acid. (7). A solution of 39.7 g (0.10 mol) of **1** 2 dioxane in 200 ml of H_2O and 200 ml of 20% KOH (0.60 mol) was heated with stirring in an apparatus designed to collect distillate in 2 N H_2SO_4. A precipitate formed in a few minutes which slowly dissolved upon distilling over the evolved ammonia. Additional water was added as needed to keep the volume at 450 ml. After 1.5 h, a total of 0.20 ml of ammonia had been collected, and a considerable amount of solid was present in the hot reaction solution. The reaction mixture was cooled to 35 °C and 425 ml of 2 N HCl was slowly added with stirring. The initial solid dissolved and another precipitate formed during the acidification. The precipitate was collected, washed with water, ethanol, and ether, and air dried to give 28.8 g (theory 27.7 g) of white, powdery **monopotassium salt of 7-carboxamido-1*H*-imidazo-[1,5-*b*]-*s*-triazole-2,5-dicarboxylic acid,** no melting point darkening at 210 °C, evolved gas at 255–260 °C. Thin layer chromatography (TLC) on cellulose using 0.2 N NH_4OH showed one major fluorescent spot with three minor slower spots. Titration required 1 equiv of base to give solution and another 1 equiv for titrating acidity of pK_a 7.40 with neut equiv 271 (theory 277).

Anal. Calcd for $C_7H_4N_5O_5K$: C, 30.3, H, 1.5; N, 25.3; K, 14.1. Found: C, 30.8; H, 1.9; N, 26.2; K, 12.8.

A small sample (5 g) was purified as the dipotassium salt by taking up in 60 ml of 3% KOH and 10 ml of saturated KCl. The dark solution was saturated with CO_2 to precipitate 4.3 g of light-blue crystals. Four recrystallizations from 1:1 isopropyl alcohol–H_2O removed the blue color and gave 1.3 g of the dipotassium salt of **7** as white needles (TLC pure), no melting point, darkened by 340 °C. The pK_a (spectrophotometric) = 0.93, 3.66, 7.34 with H_3A having max at 311 nm (ϵ 12 400), 276 (9700), 221 (21 200); H_2A^- at 307 nm (ϵ 16 000), 270 (7500), 220 (19 900); HA^{2-} at 302 nm (ϵ 11 900), 268 (9300), 238 (13 400), 204 (20 000); and A^{3-} at 328 nm (ϵ 22 300), 283 (6200), 237 (21 400).

Anal. Calcd for $C_7H_3N_5O_5K_2$: C, 26.7; H, 1.0; N, 22.2; K, 24.8. Found: C, 26.7, 26.6; H, 1.1, 1.3; N, 22.4, 22.3; K, 25.1.

1-Methyl-7-carboxamido-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5-dicarboxylic Acid (8). From 7. The monopotassium salt (2.72 g, 10 mmol) of **7** suspended in 35 ml of H_2O was dissolved by adding 6 N NaOH. Dimethyl sulfate (15 g, excess) and 6 N NaOH were added over 3 h with stirring at 36 °C while maintaining the pH between 9 and 10. After stirring overnight, the solution (pH 9.5) was heated to boiling, filtered, and acidified with 20 ml of 2 N HCl. The resulting precipitate was collected and washed with water to give 1.75 g (69%) of white, powdery **8**, evolved gas at 180 °C changing from powder to a crystalline form and then melted at 280–283 °C (darkening 260–280 °C). This material was identical (ir, TLC, and uv) with material obtained below.

From 3. In a 300-ml flask, equipped with a magnetic stirrer, addition funnel, and Claisen distillation head, was placed 11.82 g (60 mmol) of pure 1-methyl-1*H*-imidazo-[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile (**3**). A NaOH solution (7.30 g, 180 mmol, in 100 ml of H_2O) was added in one portion. Heating the mixture caused rapid solution followed by formation of precipitate. After 1.5 h, 20 ml of distillate was collected in 2 N H_2SO_4 and shown to contain 119.3 mmol of evolved ammonia. The reaction mixture was diluted with 100 ml of EtOH and cooled to 5 °C. The product was collected and washed with 100 ml of 50% ethanol, 100 ml of absolute EtOH, and ether. Air drying gave 18.04 g of the disodium salt of **8** as a white, fluffy solid, no mp below 400 °C. An analytical sample was obtained by two recrystallizations from 1:1 EtOH–H_2O (1 g in 70 ml) followed by vacuum drying at 80 °C overnight. Two different solvated modifications were sometimes obtained with different ir spectra, but reverted to the same material upon drying: NMR (D_2O,Me_4Si external) δ 4.73 (DOH exchange peak, wt 2.3) and 4.16 (wt 3).

Anal. Calcd for $C_8H_5N_5O_5Na_2$: C. 32.3; H, 1.7; N, 23.6; Na, 15.5. Found: C, 31.7, 31.7; H, 1.9, 1.7; N, 23.8, 23.7; Na, 15.1.

The disodium salt was converted to the free acid by dissolving 1.0 g in 50 ml of warm (60 °C) H_2O and acidifying with 2 N HCl until pH 1. The light cream precipitate (monohydrate by analysis) was collected and dried at 64 °C to give 0.69 g of **8**, evolved gas at 175–180 °C and melted with some decomposition at 275–280 °C. Drying at higher temperatures caused slow loss of CO_2. Uv (pH 7 and 10) max 302 nm (ϵ 14 200), 273 (sh, 8900), and 250 (13 900); (pH 3) max 307 nm (ϵ 16 400), 272 (6600), and 247 (12 700); (2 N HCl) max 313 nm (ϵ 12 300), 278 (9900), 245 (sh, 12 900), and 224 (17 900); pK_a (spectrophotometric) = 0.99 and 3.78.

Anal. Calcd for $C_8H_7N_5O_5$: C, 35.4; H, 3.4; N, 25.8; neut equiv, 135.5. Found: C, 35.3; H, 3.6; N, 25.6; neut equiv, 137, 138.

Reaction of 8 with Diazomethane. To a slurry of 253 mg (1 mmol) of **8** in 20 ml of ethanol was added 3 mmol of ethereal diazomethane. After stirring for 2 days, the solid phase was collected and washed with benzene to give 191 mg of **dimethyl 7-carboxamido-1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5-dicarboxylate (9),** mp 198–200 °C dec. An analytical sample, mp 218–219 °C dec, was obtained by recrystallization from DMF–H_2O and drying overnight at 64 °C: uv (H_2O and 2 N HCl) max 315 nm (ϵ 11 600), 280 (11 300), and 228 (19 600); NMR (CF_3COOH, Me_4Si external) δ 4.12 (wt 3) and 3.76 (wt 6).

Anal. Calcd for $C_{10}H_{11}N_5O_5$: C, 42.7; H, 4.0; N, 24.9. Found: C, 42.2; H, 4.4; N, 25.0, 24.7.

7-Carboxamido-1*H*-imidazo[1,5-*b*]-*s*-triazole-2- (or 5-) carboxylic Acid (19). A 150-ml solution of the monopotassium salt of **7** was prepared by dissolving 10 g (33 mmol by titration) of the crude salt in water to which enough dilute KOH was added to give a clear solution and carefully adjusting the pH to exactly 5.60. The clear, light-blue solution was then heated to reflux for 3 h under N_2. (In air, there was considerable darkening.) The pH had changed to 9.4. The still-hot solution was acidified with 2N HCl to pH 6 and cooled. The solid was collected, washed with water and ethanol, and dried to give 7.65 g of crude **potassium 7-carboxamido-1*H*-imidazo[1,5-*b*]-*s*-triazole-2- (or 5-) carboxylate.** An analytical sample was obtained as glistening platelets, mp darkening above 340 °C, by recrystallizations under N_2 from CO_2-free water. (Recrystallization in air gave blue crystals.) The product was dried at 80 °C for 15 h, uv max (H_2O) 280 nm (ϵ 6120) and 255 (12 700).

Anal. Calcd for $C_6H_4N_5O_3K{\cdot}H_2O$: C, 28.7; H, 2.4; N, 27.9; K, 15.6. Found: C, 29.0, 28.9; H, 2.3; N, 27.4, 27.6; K, 15.3.

The free acid **19** was prepared by acidification of a dilute solution of the monopotassium salt. The precipitate was collected, washed, and dried at 80 °C for 6 h to give a white, amorphous powder, no mp <350 °C (darkened at 260 °C); uv (pH 1) max 279 nm (ϵ 7200) and 240 (shoulder, 8000); (pH 10) max 310 nm (ϵ 13 900) and 263 (7400). Potentiometric titration indicated two buffer zones with pK_a = <4 and 7.25 with neut equiv 189 and 194, respectively (theory, 195).

Anal. Calcd for $C_6H_5N_5O_3$: C, 36.9; H, 2.6; N, 35.9. Found: C, 36.8; 36.4; H, 2.8, 3.1; N, 34.9, 35.6, 35.8.

7-Carboxamido-1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2- (or 5-) carboxylic Acid. 19 (3.1 g) was dissolved in 25 ml of water and 6 N NAOH. Dimethyl sulfate (15 ml excess) and 6 N NaOH were added in alternate small portions while maintaining the pH between 9 and 10 and the temperature at 35 °C. The solution was acidified to pH 4 with 2 N HCl and the product collected. The crude product was taken up in 50 ml of hot 0.1 N NaOH, acidified to pH 7, and cooled. The **sodium 7-carboxamido-1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2- (or 5-) carboxylate** was collected, washed, and dried to give 1.85 g of white needles, no mp <400 °C. An analytical sample was recrystallized from water: NMR (CF_3COOH, Me_4Si external) δ 8.67 (wt 1) and 4.13 (wt 3).

Anal. Calcd for $C_7H_6N_5O_3Na$: C, 36.4; H, 2.6; N, 30.3. Found: C, 36.0, 36.0; H, 3.0, 3.1; N, 30.3, 30.7, 30.5.

The free acid was prepared by acidifying a warm solution of the salt with 2 N HCl and cooling. The solid was collected, washed, and dried

at 64 °C for 8 h to give the acid as small cubes: evolves CO_2 at 195 °C and melts with decomposition at 270 °C; uv (pH 7) max 261 nm (ε 12 400) and 285 (sh, 7900); (2 N HCl) 285 nm (ε 6200) and 244 (8300). Attempts to determine the pK_a spectrophotometrically were unsuccessful giving a wide range of values (1.20–1.60) with shifts of the maxima indicating further protonation in the strong acids.

Anal. Calcd for $C_7H_7N_5O_3$: C, 40.2; H, 3.4; N, 33.5; neut equiv, 209. Found: C, 40.0, 39.7; H, 3.5, 3.5; N, 33.5; neut equiv, 208.

Hydrolysis of 7 with Acid. A mixture of 14.0 g (50 mmol) of the monopotassium salt of **7**, 100 ml of water, and 42.0 ml of 6 N H_2SO_4 was placed in a 500-ml flask fitted with a reflux condenser leading to three gas scrubbing towers in series with 100 ml of 1.0 N NaOH solution in each. A slow N_2 sweep was maintained through a tube leading down the condenser. The reaction mixture (thick slurry) was then heated to reflux for 12 h. After 3 h, the initially rapid gas evolution appeared to subside and a clear solution (5 h) gradually formed. Analyses of the trapping solutions indicated the evolution of 147 mmol of carbon dioxide (3 equiv).

The hot, clear reaction solution was then diluted with ethanol until turbid (300 ml) and cooled. The crystalline solid mixture of needles and amorphous powder was collected and dried to give 3.86 g of potassium sulfate with some ammonium ion present (ir and titration). The mother liquors were warmed and diluted with additional ethanol (total volume 1 l.) until turbid. Cooling afforded 7.43 g of crude **3-aminomethyl-1,2,4-triazole H_2SO_4 (20).** An additional 3.22 g was obtained from workup of the mother liquors. An analytical sample was prepared by three recrystallizations from 85% ethanol (100 ml/g) and dried at 80 °C for 5 h: NMR (D_2O, Me_4Si external) δ 8.88 (wt 1), 4.86 (DOH, wt 5.4), and 4.47 (wt 2). Potentiometric titration indicated three buffer zones corresponding to <4, 7.8 and 9.9 with neut equiv values of 204, 204, and 190, respectively (theory, 196).

Anal. Calcd for $C_3H_8N_4O_4S$: C, 18.4; H, 4.1; N, 28.6; S, 16.3. Found: C, 18.1, 18.3; H, 4.1, 4.1; N, 28.1, 28.4; S, 16.6, 16.4.

In another experiment the original hydrolysis solution was distilled to a low volume, fresh water was added, and the solution was redistilled successively until no more acid was collected in the distillate. There was obtained 99% of 1 equiv of volatile acid per mole of starting material. Concentration to dryness of the resulting titrated solution gave sodium formate (identified by ir).

The free base **20** was isolated by dissolving the crude H_2SO_4 salt (10.0 g) in 150 ml of H_2O and 35 ml of 6 N NaOH. The solution was boiled until no more ammonia was evolved. The pH was then adjusted to 9.00 with 2 N H_2SO_4. Concentration of the clear solution to dryness followed by sublimation (130 °C, 0.1 mm) afforded 4.25 g of **3-aminomethyl-1,2,4-triazole (20)** as a very water-soluble white solid: mp 104–143 °C; NMR (D_2O, Me_4Si external) δ 8.13 (wt 1), 4.74 (DOH, wt 3), and 3.92 (wt 2); MS parent at *m/e* 98 and base peak at *m/e* 30 ($NH_2CH_2^+$) with other strong peaks at *m/e* 28, 42, 70 ($P - N_2^+$), and 97 ($P - H^+$).

Anal. Calcd for $C_3H_6N_4$: C, 36.7; H, 6.2; N, 57.1. Found: C, 37.0, 36.8; H, 6.0, 6.0; N, 57.4, 57.4, 57.5.

Oxidation of 20. The crude 3-aminomethyl-1,2,4-triazole H_2SO_4 (4.66 g) in 50 ml of 3 N NaOH was oxidized by adding 7.95 g of potassium permanganate in small portions while stirring and heating on a hot plate for 1 hr. The clear basic filtrate was acidified first to pH 4, and then an additional 6.0 ml of 6 N H_2SO_4 was added to give a precipitate. The 1,2,4-triazole-3-carboxylic acid (**21**) was collected, washed, and dried to give 2.31 g (86%) of fine white needles, mp 140 °C with evolution of gas (reported[10] 137 °C); NMR (D_2O with 1 drop NaOH) δ 8.33 and 4.86 (DOH).

This structure was confirmed by decarboxylation at 140 °C and sublimation of the residue to give 1,2,4-triazole (**22**), mp 120 °C (reported[10] 121 °C), identified by its ir spectrum.[12]

1-Methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-7-carboxamide (10). 8 monohydrate (705 mg, 2.60 mmol) was placed in a micro sublimer and covered with a loose cotton plug. Sublimation under vacuum at 180–240 °C was accompanied by initial CO_2 evolution to give 306 mg (71%) of **10**, mp 281–285 °C dec. Two recrystallizations from water (7.5 ml) followed by sublimation at 210–220 °C gave an analytical sample (217 mg): mp 289–292 °C dec; uv (pH 7 and 12) max 276 nm (ε 17 000) and (pH 1) max 273 nm (ε 15 200) and 232 (6900); NMR (CF_3COOH, Me_4Si external) δ 8.68 (wt 1), 8.17 (wt 1), and 3.89 (wt 3); (D_2O at 80 °C, Me_4Si external) δ 8.17 (wt 1), 7.79 (wt 1), 4.33 (DOH, wt 2.5), and 4.00 (wt 3); MS parent at *m/e* 165 and base at *m/e* 109. (From the MS of **10** containing CD_3 group, this peak contains the CD_3 group and is $P - CCONH_2^+$.)

Anal. Calcd for $C_6H_7N_5O$: C, 43.6; H, 4.3; N, 42.4. Found: C, 43.8; H, 4.4; N, 42.3, 42.1.

When the above reaction was carried out on a larger scale (12–15 g), the sublimation required 5–6 days to give **10** in 65% yield. Attempts to isclate **10** from the crude decarboxylated mixture by recrystallizations resulted in severe loss.

10 appears to form a crystalline hydrochloride when recrystallized from HCl which reverts to free amide on treatment with $NaHCO_3$. Potentiometric titration gave a pK_a of 1.82 ± 0.04 but this may be a mirage[13] (5×10^{-3} N at halfway titration).

Under the same conditions, decarboxylation of 1-methyl-7-carboxamido-1*H*-imidazo[1,5-*b*]-*s*-triazole-2- (or 5-) carboxylic acid (**19**) gave **10.**

1-Methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-7-carbonitrile (11). A mixture of 1.65 g (10 mmol) of **10** and 12 ml of phosphorus oxychloride was refluxed for 2 h. The original thin slurry became very thick with solid which slowly dissolved to give a black solution. The excess phosphorus oxychloride was removed under vacuum and the tarry residue was treated with 12 ml of ice and water. The black solution was neutralized to pH 7.0 with dilute NaOH. The greenish solid was collected, washed, and dried to give 0.78 g (53%) of crude **11.** Sublimation (160 °C, 0.05 mm) removed the color. An analytical sample, mp 219–220 °C, was obtained by recrystallizations from dichloroethane (90 ml/g) followed by sublimation: uv (pH 1 and 11) max 260 nm (ε 12 200) and 235 (10 400); (2 N HCl) max 265 nm (ε 21 000) and 227 (7000); ir (KBr C≡N at 2205 (s), C=C and C=N at 1620 (s), 1570 (w), and 1520 (m), with other strong bands at 1185, 1080, 1060, and 860 cm^{-1}; NMR (CD_3COCD_3, Me_4Si external) δ 7.76 (wt 1), 7.25 (wt 1), and 3.33 (wt 3); MS *m/e* 147 (parent, base), 15, 28, 41 (CHN_2^+), 53, 68, 77 ($P - C_2H_4N_3^+$), 91 ($P - C_2H_4N_2^+$), 107, and 120 ($P - HCN^+$).

Anal. Calcd for $C_6H_5N_5$: C, 49.0; H, 3.4; N, 47.6. Found: C, 48.7, 48.8; H, 3.2, 3.3; N, 47.8, 47.9, 48.4.

Using CF_3OOH as a solvent, peaks were at δ 8.70, 8.16, and 3.64 in a ratio of 1:1:4. The latter peak was resolved to two peaks with a 2.2-Hz separation. Dilution with D_2O caused the δ 3.64 peak to coalesce to one peak but the relative area remained 4. Apparently, trifluoroacetic acid reacted with the compound to give a new CH bond (nonexchangeable).

Acetylation of 10. A mixture of 200 mg of **10** and 5 ml of acetic anhydride was refluxed until solution occurred. The solvent was evaporated and the residue sublimed to give 236 mg of **acetyl 1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-7-carboxamide,** mp 207–212 °C. An analytical sample, mp 220–221 °C, was obtained by recrystallization from water: uv (pH 1) max 297 nm (ε 20 600) and 239 (3600); (pH 7) max 299 nm (ε 23 600) and 250 (2900); (pH 11) max 298 nm (ε 17 500) and 286 (sh, 16 000, concentration dependent); NMR (CF_3COOH, Me_4Si external) δ 8.20, 7.70, 3.43, and 1.65 (wt 1:1:3:3, respectively); MS parent at *m/e* 207* with base peak 149* ($P - CH_3CONH^+$), other strong peaks at 15*, 28, 42*, 43, 53, 109*, 122*, 136*, 165*, and 192*. (Peaks marked contain the NCH_3 group as shown by the MS of the NCD_3 compound.)

Anal. Calcd for $C_8H_9N_5O_2$: C, 46.4; H, 4.4; N, 33.8. Found: C, 46.4, 46.2; H, 4.4, 4.4; N, 33.9.

Acidifying the pH 11 uv solution showed that no change had occurred. However, dissolving the acetyl compound in hot 1 N sodium carbonate caused a rapid precipitation of the unacetylated material **10.**

Rearrangement of 10 to 3-Methylguanine (13). A mixture of 990 mg (6 mmol) of **10** and 30 ml of 0.5 N NaOH was heated at reflux for 1 h (reaction complete after 30 min). The solution was cooled and acidified to pH 7.0 with 1 N HCl. The precipitate was redissolved by heating and adding more water (total volume 90 ml). After cooling 883 mg of 3-methylguanine (**13**) was obtained as small needles, mp 366–371 °C dec. Two recrystallizations from water raised the melting point to 375–377 °C dec. An analytical sample was dried at 80 °C for 7 h: uv (pH 1) max 265 nm (ε 10 600), 245 (sh, 7250), and (pH 11) 247 nm (ε 14 100) [reported[6] (pH 1) 265 nm (ε 10 900), 245 (sh, 8060), and 274 (13 000)]; pK_a (potentiometric, concentration 4.44 M, halfway) 4.41 ± 0.02 and 9.60 ± 0.04; (spectrophotometric) 4.43 and 9.62; NMR (0.1 N NaOD, Me_4Si external) δ 7.47 (wt 1), 4.86 (DOH), and 3.27 (wt 3).

The material was identical with 3-methylguanine obtained from Cyclo Chemical Corp. Los Angeles, Calif., by uv, ir, MS, and paper chromatography (Whatman No. 1, *n*-BuOH saturated with H_2O, ammonia atmosphere, $R_{adenine}$ 0.53, 0.52).

Anal. Calcd for $C_6H_7N_5O$: C, 43.6; H, 4.3; N, 42.4. Found: C, 44.0, 43.8; H, 4.5, 4.3; N, 42.4.

Registry No.—**1**, 58520-76-8; **3**, 58502-13-9; **4**, 58502-14-0; **5**, 58502-15-1; **6** Na salt, 58502-16-2; **7** mono-K salt, 58502-17-3; **7** di-K salt, 58502-18-4; **8**, 58502-19-5; **8** di-Na salt, 58502-20-8; **9**, 58502-21-9; **10**, 58502-22-0; **10** acetyl derivative, 58502-23-1; **11**, 58502-24-2; **13**, 2958-98-7; **19** 2 isomer, 58502-25-3; **19** 2 isomer K salt, 58502-26-4; **19**

5 isomer, 58502-27-5; **19** 5 isomer K salt, 58502-28-6; **20**, 15285-16-2; **20** H_2SO_4, 58502-30-0; **21**, 4928-87-4; sodium C_7N_7, 58502-31-1; tetramethylammonium C_7N_7, 58502-33-3; zinc $(C_7N_7)_2$, 58502-34-4; lithium C_7N_7, 58502-35-5; manganous $(C_7N_7)_2$, 58502-36-6; cupric $(C_7N_7)_2$, 58502-37-7; silver C_7N_7, 58502-38-8; tetraethylammonium C_7N_7, 58502, 39-9; trimethylactadecylammonium C_7N_7, 58502-40-2; *N*-methylphenazinium C_7N_7, 58526-69-5; trimethylsulfonium C_7N_7, 58502-42-4; methyltriphenylphosphonium C_7N_7, 58502-43-5; HC_7N_7, 58502-44-6; potassium cyanide, 151-50-8; cyanogen, 2074-87-5; sodium cyanide, 143-33-9; tetramethylammonium chloride, 75-57-0; zinc carbonate, 3486-35-9; 1-chloro-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile, 58502-45-7; 1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarboxamide, 58502-46-8; dimethylformamide, 68-12-2; 1-benzyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2,5,7-tricarbonitrile, 58502-47-9; benzyl chloride, 98-88-4; diazomethane, 334-88-3; 7-carboxamido-1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2-carboxylic acid, 58502-48-0; 7-carboxamido-1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-5-carboxylic acid, 58502-49-1; sodium 7-carboxamido-1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-2-carboxylate, 58502-50-4; sodium 7-carboxamido-1-methyl-1*H*-imidazo[1,5-*b*]-*s*-triazole-5-carboxylate, 58502-51-5.

References and Notes

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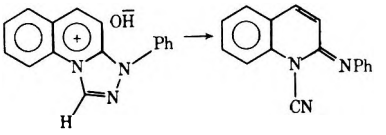

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Rearrangement of *N*-Acylaziridines in Strong Acid Media[1]

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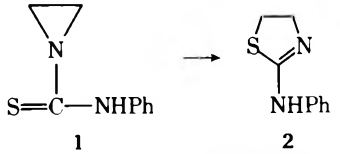
The rearrangement of *trans*-1-*p*-nitrobenzoyl-2,3-dimethylaziridine (**8**) in either sulfuric or fluorosulfuric acid occurs stereoselectively to give the *trans*-2-phenyl-4,5-dimethyloxazolinium cation and after neutralization the trans oxazoline **10**. In contrast, the isomeric cis aziridine derivative **7** gives a mixture of the cis and trans oxazolines, **9** and **10**, respectively, in a 28:72 ratio. These results implicate acyclic carbocationic intermediates in the rearrangement. The mechanism of the acid-catalyzed isomerization of acylaziridines is discussed in light of these results and other available data.

Gabriel and Stelzer[2] reported the acid-catalyzed isomerization of thioacylaziridines in 1895. Their report described the conversion of the thiourea derivative **1** to the thiazoline **2** upon heating the former in concentrated hydrochloric acid.

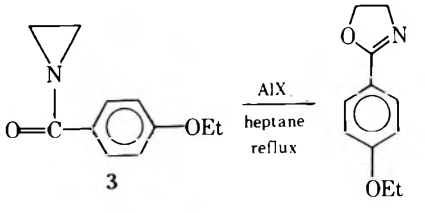


(1)

1 **2**

The reaction lay dormant until the late 1950s when a number of workers confirmed[3] and extended[4,5] the reaction.[6] One of these reports included isomerizations of several aziridines utilizing other aqueous mineral acid catalysts.[5]

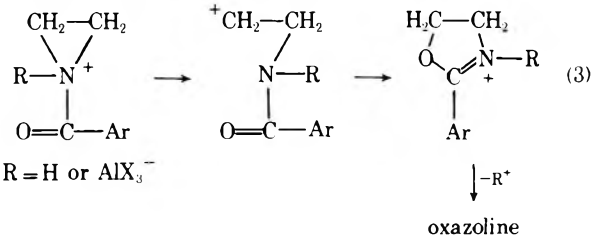
Heine and Proctor[7] carried out a similar isomerization on acylaziridines using aluminum halides in refluxing heptane, eq 2. Two mechanisms for the isomerization were considered;



(2)

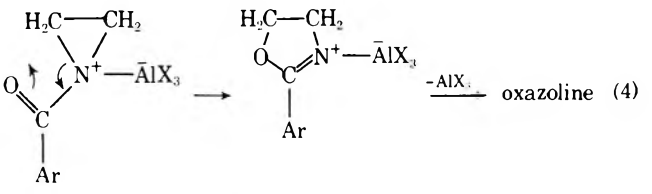
3

one involved sequentially acid attack at nitrogen, ring opening, and cyclization, eq 3; the second involved a four-centered transition state, eq 4. Owing to the low dielectric constant of



(3)

oxazoline



(4)

the solvent (heptane) and the high energy of the primary carbocationic intermediate formed from *N*-(*p*-ethoxybenzoyl)aziridine (**3**), Heine and Proctor[7] preferred the mechanism shown in eq 4 for the isomerization of **3**.

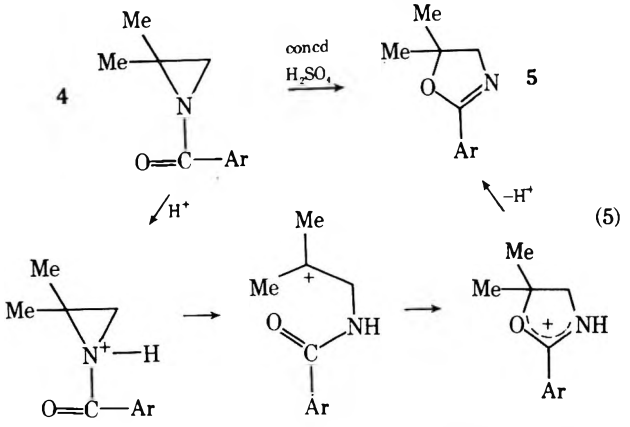
In subsequent work, Heine et al.[8] used concentrated sulfuric

Table I. NMR Data for 7, 8, 9, and 10[a,b]

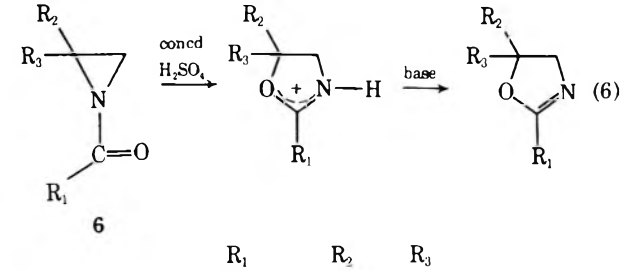
Compd	Aryl protons	Methyl protons	Ring protons
7	8.16 (d), J = 9.1 8.23 (d), J = 9.1	1.35 (d), J = 5.5	2.66 (m)
8	8.10 (d), J = 9.0 8.24 (d), J = 9.0	1.23 (d), J = 5.2	2.56 (m)
9	8.09 (d), J = 9.0 8.25 (d), J = 9.0	1.25 (d), J = 6.4 1.38 (d), J = 6.0	4.52 (m, NCH) 4.89 (m, OCH)
10	8.04 (d), J = 8.7 8.14 (d), J = 8.7	1.31 (d), J = 6.7 1.42 (d), J = 6.0	3.86 (m, NCH) 4.33 (m, OCH)

[a] Values are in parts per million from internal Me_4Si. Spectra were taken on Varian EM-360 and HA-100 spectrometers in $CDCl_3$. [b] d = doublet; m = multiplet.

acid as the medium for isomerizing 1-*p*-nitrobenzoyl-2,2-dimethylaziridine (**4**) to 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline (**5**) in 97% yield. The sole formation of **5** and not the 4,4-dimethyl isomer was taken as evidence for scission of a C–N bond in a protonated aziridine. The mechanism shown in eq 5 was suggested to account for the observed reaction.



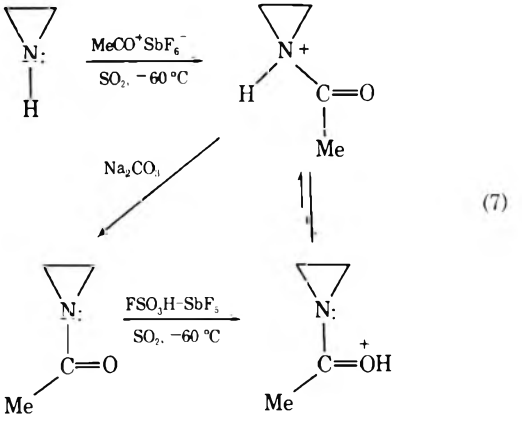
We have shown in an earlier paper[9] that *N*-acylaziridines (**6a–f**) rearrange to oxazolinium cations upon their introduction into strong acid media,[9–11] eq 6, and these ions are



	R_1	R_2	R_3
a	CH_3	H	H
b	CH_3	CH_3	H
c	CH_3	CH_3	CH_3
d	C_6H_5	H	H
e	C_6H_5	CH_3	H
f	*p*-$NO_2C_6H_4$	CH_3	CH_3

stable[11,12] until neutralization by aqueous base. Demonstration of acyclic carbocationic intermediates or of N-protonated acylaziridines as precursors to oxazolinium ions in these isomerizations has not been achieved.

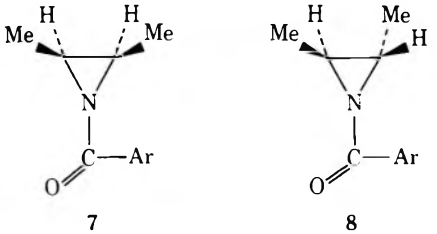
Olah and Szilagyi[13] have prepared N-protonated acylaziridines from the reaction of aziridine and acylium salts, eq 7. Conversely, direct protonation of acylaziridines at low temperature provides, as the only protonated species (by NMR analysis), the O-protonated acylaziridine.[9,13] Olah and Szilagyi[13] suggested that an equilibrium exists between the O-protonated and the N-protonated forms (see eq 7), but did not produce compelling evidence in favor of it.



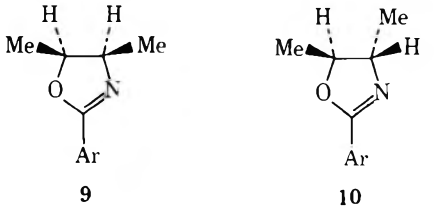
The present study of the acid-catalyzed rearrangement of *cis*-(**7**) and *trans*-(**8**) 1-*p*-nitrobenzoyl-2,3-dimethylaziridine provides the first published account on the stereochemistry of isomerization of acylaziridines in strong acid media.

Results and Discussion

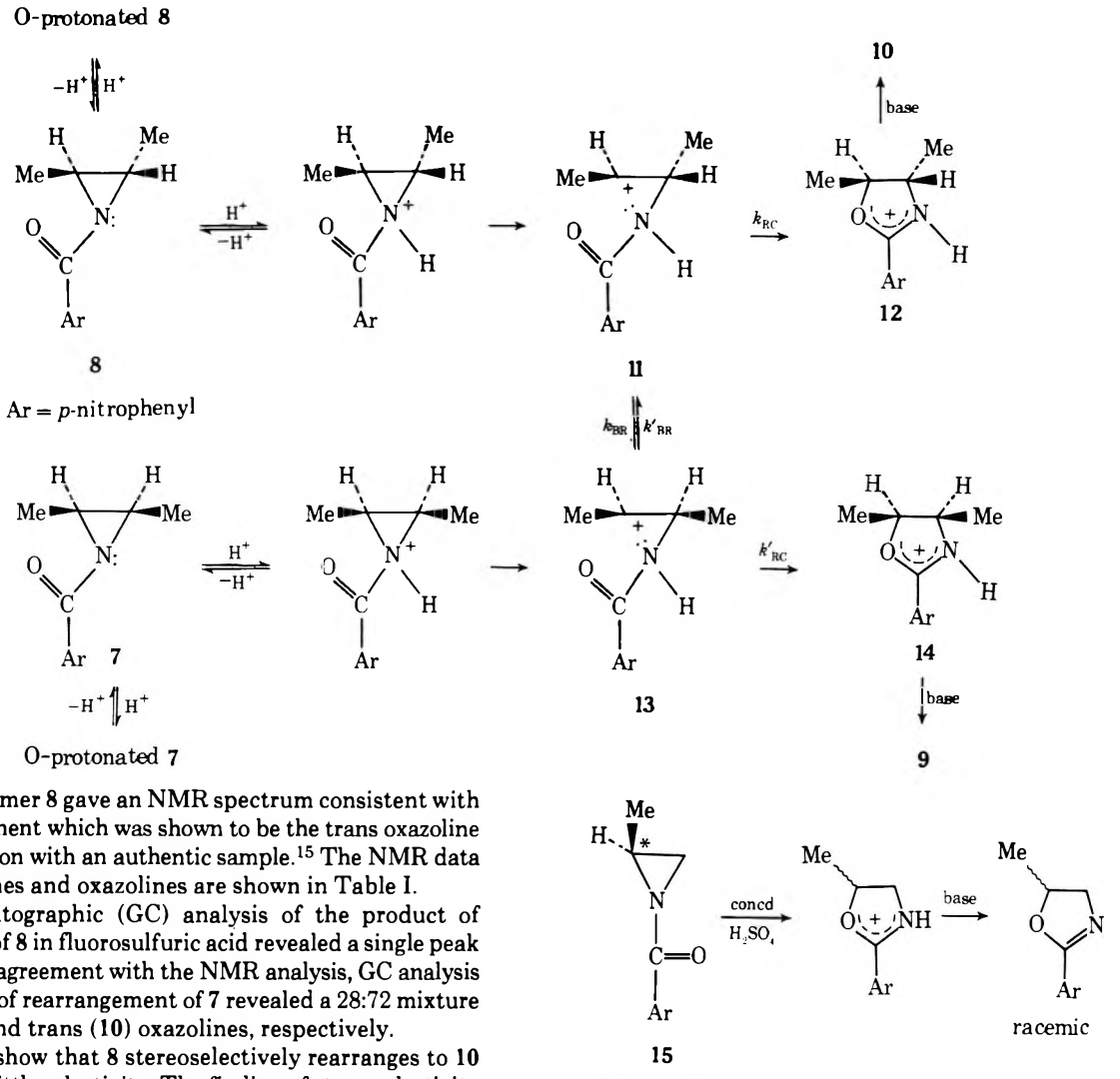
The acylaziridines **7** and **8**, dissolved in carbon tetrachloride, were readily extracted into cold 90% sulfuric acid solution or into fluorosulfuric acid resulting in solutions which gave NMR spectra characteristic of oxazolinium cations. However, the spectra were complex, making an unequivocal stereochemical assignment of the structures difficult. Therefore, the fluorosulfuric acid solutions of **7** and of **8** were drowned into cooled and rapidly stirred aqueous potassium carbonate–ether solutions.[14] Upon drying of the ether layers and removal of the ether, the resulting oxazolines were obtained. Analysis of the NMR spectra of the products was performed. The NMR spectrum of the rearrangement products of the cis isomer **7** was complex; however, it was interpreted by assuming that a mixture of **9** and **10** was present. The isomerization product



Ar = *p*-nitrophenyl



Scheme I



of the trans isomer **8** gave an NMR spectrum consistent with a single component which was shown to be the trans oxazoline **10** by comparison with an authentic sample.[15] The NMR data for the aziridines and oxazolines are shown in Table I.

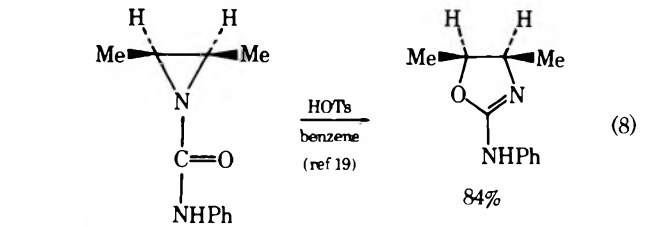
Gas chromatographic (GC) analysis of the product of isomerization of **8** in fluorosulfuric acid revealed a single peak due to **10**.[15] In agreement with the NMR analysis, GC analysis of the product of rearrangement of **7** revealed a 28:72 mixture of the cis (**9**) and trans (**10**) oxazolines, respectively.

Our results show that **8** stereoselectively rearranges to **10** while **7** shows little selectivity. The finding of stereoselectivity in the rearrangement of the trans aziridine **8** and the lack of stereoselectivity in the rearrangement of the cis isomer **7** confirms Heine's suggestion of acyclic carbocation involvement as shown in eq 5. Our view of how these reactions occur is shown in Scheme I. It is reasonable to assume that these rearrangements occur via the N-protonated acylaziridines. The differences in the products can be accounted for by assessing the probable fates of the carbocations **11** and **13**. Since the trans oxazolinium ion **12** does not suffer from nonbonding interactions of the severity of those in **14**, the transition state leading to **12** should be preferred to that leading to **14**. Thus upon opening of the N-protonated aziridine ring of **8**, ring closure of the carbocation **11** to the oxazolinium ion **12** would be highly favored over bond rotation (i.e., $k_{RC} > k_{BR}$) to give carbocation **13** which subsequently could undergo ring closure to **14**. The finding of a mixture of **9** and **10** from the rearrangement of **7** indicates that bond rotation in **13** (i.e., **13** → **11**) competes with ring closure to **14** (i.e., $k'_{BR} \simeq k'_{RC}$). From these results it seems likely that if substituents substantially larger than methyl groups were present in a cis aziridine like **7**, the product upon acid-catalyzed rearrangement may well be solely the trans oxazoline.

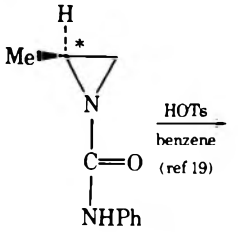
Hearn[17] has studied the isomerization of (*S*)-1-*p*-nitrobenzoyl-2-methylaziridine (**15**) in concentrated sulfuric acid and observed a significant amount of racemization.[18] His results tend to support the mechanism presented in Scheme I.

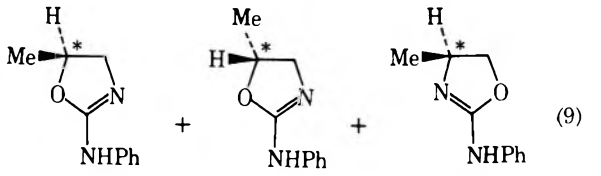
Nabeya and Iwakura and their co-workers[19,20] have investigated the stereochemistry of the acid-catalyzed isomerization of 1-carbamylaziridines to 2-amino-2-oxazoline derivatives and have obtained results which are remarkably different from ours. This is undoubtedly the result of their use of nonpolar solvents with low ionizing power whereas our solvents are highly polar and highly ionizing. Hence the SN1-like mechanism, which we propose for isomerization of acylaziridines in strong acids such as sulfuric and fluorosulfuric, is not favored in nonpolar solvents owing to the relative instability of carbocations in nonpolar media.[21] The results of isomerization with *p*-toluenesulfonic acid of some carbamylaziridines in refluxing benzene are shown in eq 8–10. Without additional evidence, one might suggest that the result shown in eq 8 is explicable by a carbocationic mechanism, that is, an intimate ion pair might result between the carbocation and the conjugate base of the acid (i.e., OTs^-). Collapse of such an ion pair in benzene would undoubtedly be rapid; hence stereochemistry might be retained. The results shown in eq 9, however, negate the above proposal as the sole mechanism. Since a portion of the product is obtained from aziridine ring opening at the less substituted carbon,[22] at least some of the product (and perhaps most of it) must arise by another mechanism. The most likely alternative mechanisms[19,20] are one similar to that shown in eq 4 and an SN2-like mechanism similar to that known for nucleophile-catalyzed isomerization of acylaziridines.[6,16] The results shown in eq 10 are best explained by the intimate ion pair mechanism.[20] Thus, when no unbound counterion is present (as in the boron trifluoride cat-

Ar = *p*-nitrophenyl

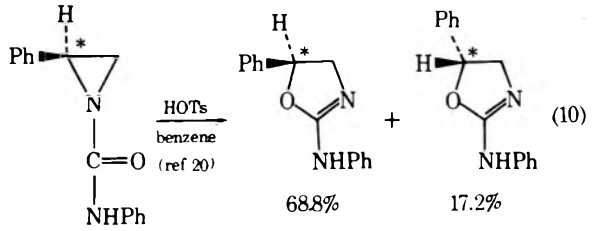


(8)





(9)



(10)

alyzed reaction), the product is nearly racemized,[20] indicating a mechanism change to one involving a free carbocation.

In summary, the acid-catalyzed isomerization of acylaziridines occurs via acyclic carbocation intermediates in strong acid media. The stereochemistry of the products appears to be determined by a competition between the rates of cyclization and of bond rotation, processes which are affected by nonbonded interactions. In nonpolar media, acyclic carbocations do not appear to be involved except where carbocation stabilizing groups, such as an aryl group, are present. In the latter cases, with protonic acids intimate ion pairs appear to be involved in determining product stereochemistry.

Experimental Section

***erythro*- and *threo*-3-Amino-2-butanol.** The isomeric 3-amino-2-butanols were prepared by the ammonolysis of the respective epoxides by the procedure previously reported.[23] A mixture of *cis*-2,3-epoxybutane and *trans*-2,3-epoxybutane (Research Organic/Inorganic Chemical Corp.) was separated by careful distillation with a Nester-Faust adiabatic annular Teflon spinning band assembly in a manner similar to that described by Dickey et al.[24] Refractionation of the purified fractions gave the trans epoxide, bp 55–56 °C (lit.[24] 54–55 °C), and the cis epoxide, bp 59–60 °C (lit.[24] bp 58–59 °C).

Reaction of the cis epoxide with excess liquid ammonia in the presence of 1 equiv of water, as described elsewhere,[23] gave a 90% distilled yield of *threo*-3-amino-2-butanol, bp 69–70 °C (20 mm). The erythro isomer was prepared in a similar fashion from the trans epoxide. The crude amino alcohol was used to prepare the trans aziridine as described below.

***cis*-1-*p*-Nitrobenzoyl-2,3-dimethylaziridine (7).** *cis*-2,3-Dimethylaziridine was prepared from *threo*-3-amino-2-butanol following the directions of Dickey et al.[24] The purified aziridine, bp 82–83 °C (lit.[24] bp 82.5–82.9 °C), was converted to the amide **7** by reaction with freshly recrystallized *p*-nitrobenzoyl chloride and triethylamine in dry benzene by the procedure of Heine et al.[16] Recrystallization from ethanol gave **7** melting at 142–143 °C (lit.[16] 143–145 °C). The NMR spectrum of **7** (see Table I) was consistent with the assigned structure.

Isomerization of 7 and 8 in 90% Sulfuric Acid. A carbon tetrachloride solution containing ca. 10% of **8** was added dropwise to an equal volume of a rapidly stirred 90% sulfuric acid solution at 10–15 °C. After about 10 min of rapid stirring below 15 °C, the sulfuric acid layer was transferred to an NMR tube and a capillary filled with tetramethylsilane was added. The NMR spectrum had peaks at δ 1.96–2.15 (6 protons, broad multiplet, CHC), 4.98–5.40 (1 proton, broad multiplet, CHN), 5.50–5.90 (1 proton, broad multiplet, CHO), 8.55 (2 protons, doublet, J = 8.5 Hz, aryl), 9.02 (2 protons, doublet, J = 8.5 Hz, aryl), and 9.76 ppm (1 proton, broad NH). This spectrum was consistent with that of oxazolinium ions **12** or **14** but was too poorly resolved to allow a definitive stereochemical assignment.

In the same manner, a small sample of **7** was dissolved in 90% H_2SO_4 and the NMR spectrum of the resulting solution was recorded. All of the peaks above plus additional peaks were present.

Isomerization of 7 and 8 in Fluorosulfuric Acid. The acylaziridines **7** and **8** each in ca. 10% carbon tetrachloride solutions were extracted into fluorosulfuric acid[9] at 0 °C using the technique described above. The acid solutions were allowed to warm to room temperature and their NMR spectra were recorded. The spectra of the protonated oxazolines in FSO_3H appeared to be very similar to the spectra of the ions in 90% H_2SO_4.

The FSO_3H solutions were neutralized by dropwise addition to rapidly stirred dispersions of aqueous potassium carbonate–ethyl ether.[14] The ether layers were dried (Na_2SO_4) and evaporated to give the crude isomerization products from **7** and from **8**.

The NMR spectrum of the dried product from the isomerization of **8** proved to be identical with that of an authentic sample[15] of **10** (see Table I). Gas chromatographic analysis on a 6 ft × 0.125 in. silicone gum W-98 column showed the isomerization product from **8** to be solely **10** (i.e., with less than 0.5% of **9**).

The dried product from the isomerization of **7** gave an NMR spectrum (in CCl_4) indicating a mixture. A comparison analysis of the spectrum of this sample with those of authentic samples of **9** and **10** (see Table I) proved the mixture to be composed of **9** and **10**. Gas chromatographic analysis under identical conditions with those above revealed the mixture to be **9** and **10** in a ratio of 28:72.

It was also shown that **9** and **10** do not equilibrate under workup or analytical conditions and that the cations in sulfuric or fluorosulfuric acid do not equilibrate.[12] It could not be unequivocally demonstrated that **7** does not partially isomerize to **8** prior to rearrangement; yet there is no evidence that this is occurring.

Acknowledgment. This work was supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society. We also kindly acknowledge a gift of authentic samples of **9** and **10** by Professor Harold W. Heine.

Registry No.—**7**, 7042-44-6; **8**, 7042-45-7; **9**, 7042-06-0; **10**, 7042-07-1; *cis*-2,3-dimethylaziridine, 930-19-8; *p*-nitrobenzoyl chloride, 122-04-3.

References and Notes

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(15) Authentic samples of **9** and **10** were provided by Professor Harold W. Heine; cf. ref 16.

(16) H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31**, 2662 (1966).
(17) R. A. Hearn, unpublished B.S. Thesis, The University of Alabama in Huntsville, Sept 1970.
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(19) T. Nishiguchi, H. Tochio, A. Nabeya, and Y. Iwakura, *J. Am. Chem. Soc.*, **91**, 5835, 5841 (1969).
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(22) Opening at the less substituted carbon has been called the "normal" mode while opening at the more substituted carbon has been called the "abnormal" mode (cf. ref 18–20). Since this terminology is backwards for carbocation reactions, its use here would be confusing. We recommend that such terminology not be perpetuated.
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Versatile Intermediates for Heteroatom-Substituted Adamantane Derivatives

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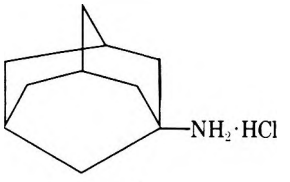
9-Acetoxybicyclo[3.3.1]nona-2,6(7)-diene (**18**), a versatile intermediate for the synthesis of heteroatom substituted adamantanes, was prepared in eight steps from the commercially available 1,4-cyclohexanediol. This intermediate may be used in the synthesis of substituted oxa-, aza-, and thiaadamantanes. Utility of this intermediate was shown by synthesis of 2-oxa-6-adamantanol (**19**), 2-oxa-6-adamantanone (**22**), 2-oxa-6-adamantanamine hydrochloride (**23**), and 2-oxa-6-adamantanecarboxylic acid (**26**).

There has been much interest in compounds containing the adamantane moiety since they exhibit many interesting medicinal properties. Adamantane derivatives have shown effectiveness against several types of viruses,[1–4] and in treatment of leukemia.[5] They were also found to be active in vitro against angeosarcoma, pancreatic sarcoma,[6] and antineoplastic activity.[7–9] Davies et al.[10] discovered the inhibitory effects of 1-adamantanamine hydrochloride (**1**) against in-



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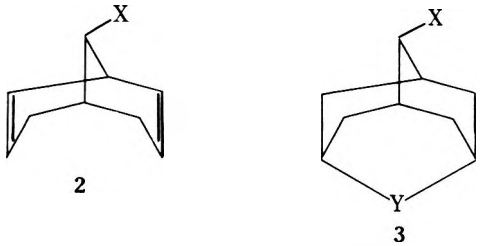
fluenza group A. 1-Adamantanamine was also found, quite by accident, to be active against Parkinson's disease.[11]

In view of the ability of adamantane to modify the biological activity of various compounds and the importance of heteroatoms in medicinal chemistry, we launched a program to synthesize adamantane derivatives with a heteroatom (oxygen, nitrogen, or sulfur) incorporated in the adamantane ring system.[12] We report here the synthesis of versatile intermediates for heteroatom-substituted adamantanes, and the synthesis of 2-oxaadamantan-6-amine and 2-oxaadamantane-6-carboxylic acid.

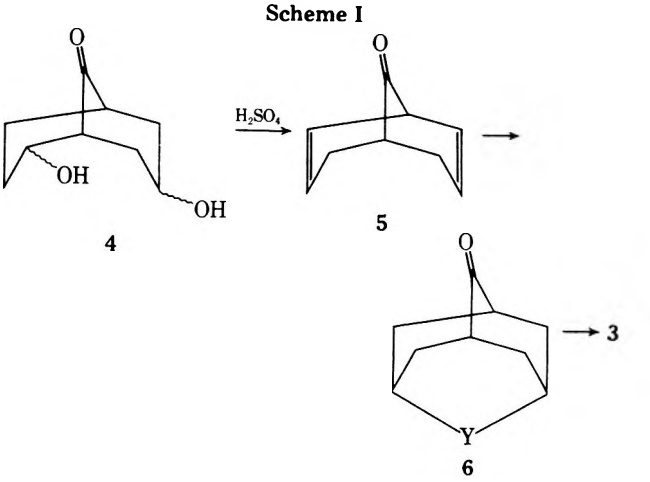
The immediate goal was to synthesize 9-substituted derivatives of bicyclo[3.3.1]nonadiene (**2**). Our long-range goal was to synthesize 2-substituted heterocyclic compounds **3** of the adamantane series through the intermediacy of compound **2**. The envisioned synthesis that was proposed for the aforementioned goals is depicted in Scheme I.



2 **3**

X = OH, OTs, NH_2, COOH
Y = O, N, S

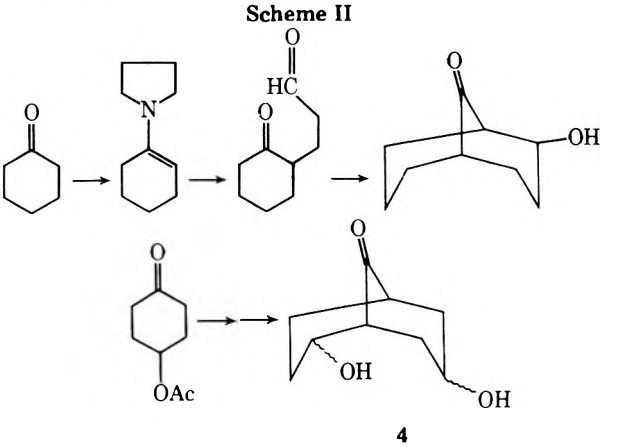
Scheme I



4 **5** **6**

Our plans for accomplishing the synthesis of the diol **4** involved modification of a procedure originally worked out by Cope[13] and Woodward.[14] If these procedures were now applied to 4-acetoxycyclohexanone, compound **4** should result (Scheme II).

Scheme II



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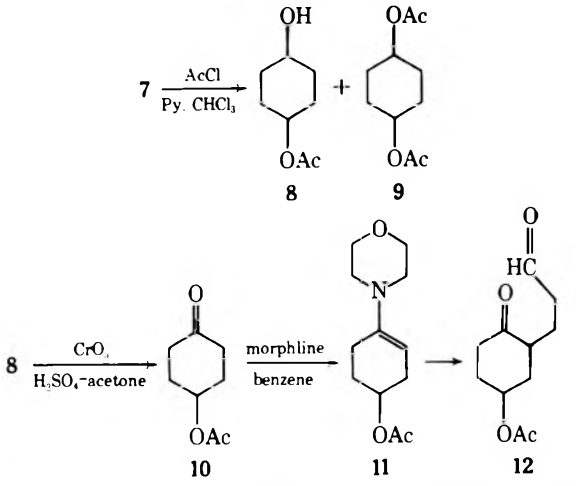
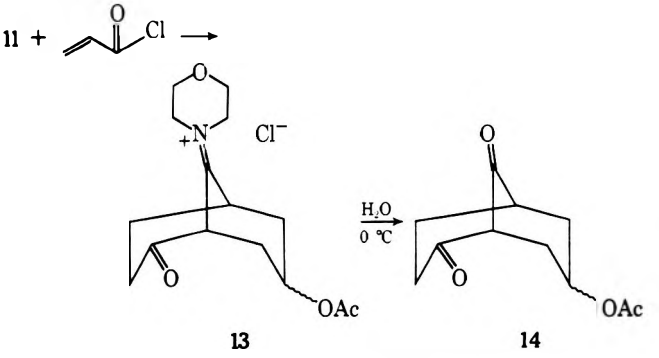
We found that the acetate 8 could be produced in excellent yield by the direct acetylation of quinitol (7) with acetyl chloride and pyridine. Reactions with acetic anhydride gave inferior results. Although the ratio of 8 to 9 (Scheme III) was

Scheme III



65:35 when 1 mol of quinitol was used per mole of acetyl chloride, this ratio increased to 87:13 when a 2.4 molar excess of quinitol was used. Use of excess reagent causes no isolational problems since quinitol is soluble in water and practically insoluble in chloroform. It was not necessary to remove the diacetate 9 from 8 since the presence of 9 did not interfere with the subsequent reaction in which 8 and 9 had to be utilized. Furthermore, 9 could be removed from the acetoxy enamine 11 by fractional distillation. Oxidation of the mixture of 8 and 9 with Jones reagent gave 10 in good yield in addition to the unchanged diacetate 9.

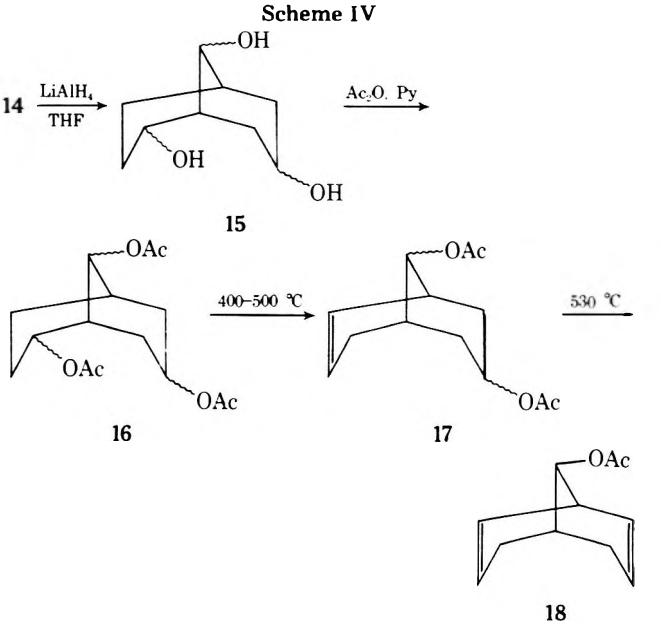
Hickmott[15] has worked out a procedure in which morpholinocyclohexene, when treated with acryloyl chloride, produces bicyclo[3.3.1]nonane-2,9-dione directly. A bicyclic dione can be produced even if the 3 and 4 positions of the enamine are fused to another ring system.[16] By applying the Hickmott procedure to the enamine 11, we were able to synthesize in good yield the bicyclic acetoxy dione 14 depicted below.



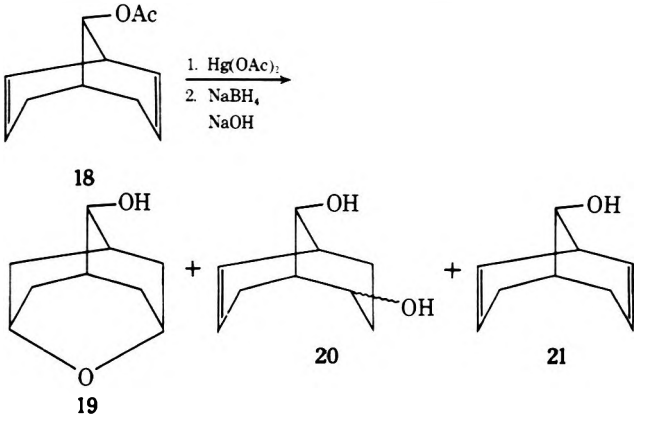
The procedure adopted for synthesis of the bicyclic diene 18 is depicted in Scheme IV. The dione 14 was reduced to the corresponding triol 15, which was converted to the triacetate 16. Pyrolysis of the triacetate 16 was best accomplished as a two-step sequence. In the first step the neat syrup was heated at 400–500 °C in a Pyrex test tube and the product, which consisted mainly of the monoolefin 17, was collected as a distillate. Pyrolysis of 17 in the vapor phase over glass beads led to the dienyl acetate 18 which could be isolated in relatively pure form by distillation. The overall yield of 18 from the diol 7 was 2.3%.

Cyclization. Our first step after the synthesis of the diene was cyclization to the oxaadamantane structure. Four meth-

Scheme IV



ods were tried with this diene. Treatment of the bicyclic diene with mercuric acetate in a THF/water solvent system[17] gave the oxaadamantanol 19 in about 25% yield. Attempts to reduce the amounts of side products by longer reaction time did not increase the yield of oxaadamantanol. Separation was ac-



complished using an alumina column. Preparative gas chromatography was also used to separate these compounds.

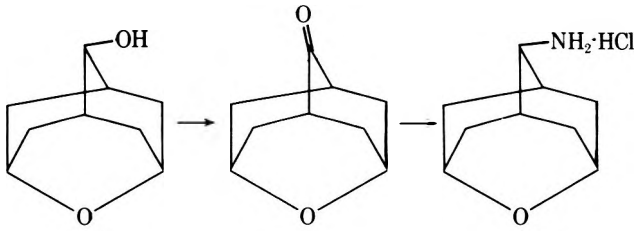
A method which showed great promise because of the lack of side products was treatment of the bicyclic diene 18 with mercuric acetate in water.[18] Gas chromatography showed that 19 was 90% of the product, but was isolated only in 10% yield.

Another method given much consideration in the early stages of the research was the addition of bromine in 10% KBr in water,[19] followed by a two-step reduction. The bromines were removed by treatment with Raney nickel and the acetoxy group was reduced with lithium aluminum hydride. This method was successful on a small scale, 100–200 mg of the diene 18. However, attempts to duplicate on a larger scale, 1-g quantity, proved unsuccessful.

The refluxing of the bicyclic diene with formic acid provided another possible route.[20] The number of side products, somewhat more plentiful than expected, made this an unacceptable procedure.

2-Oxa-6-adamantanamine Hydrochloride. The oxidation of oxaadamantanol 19 by Jones reagent provided a very efficient method[21] for obtaining the ketone 22 in yields of 90–97%. From the ketone 22, we considered two possible routes to the amine hydrochloride 23: reductive amination and the formation of the oxime followed by reduction of the amine.

Catalytic hydrogenation of adamantanone with Raney



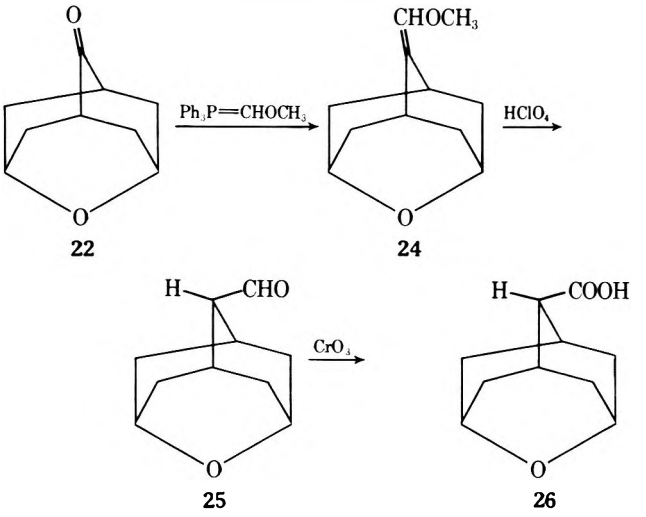
19 22 23

nickel, under 50 psi hydrogen pressure in ethanol saturated with ammonia, gave the amine in 15% yield. Excess ammonia was used to prevent the formation of secondary amines. The low yield of the amine was due to the formation of adamantanol as a side product. A less active catalyst was sought. Ten percent palladium on carbon was found to work well, producing yields of about 65%. When the same procedure was applied to oxaadamantanone **22**, a yellow oil was obtained, which was not crystallized, but converted directly to the amine hydrochloride, purified by sublimation in a 60% yield.

Our effort to reduce adamantanone oxime to the amine, either with lithium aluminum hydride or diborane in diglyme, was unsuccessful.

Carboxylic Acid. Alberts, Wynberg, and Strating reported[22] supposedly the best method of converting 2-adamantanone to 2-adamantanecarboxylic acid. Their method, modified for our system, is shown in Scheme V. The aldehyde

Scheme V



22 24 25 26

25 was oxidized by Jones reagent to the oxaadamantanecarboxylic acid **26**. The yield of acid from ketone **22** was 20%.

Experimental Section[23]

Acetylation of 1,4-Cyclohexanediol. The diol **7** (400 g, 3.4 mol) in 1.1 l. of chloroform and 1.0 l. of dry pyridine was chilled to 0 °C and to it was added, with rigorous mechanical stirring over a period of 9.5 h, a solution of 110 ml (121 g, 1.5 mol) of acetyl chloride in 0.6 l. of chloroform. Stirring overnight resulted in a clear golden yellow solution which was neutralized at 0 °C by the addition of 1.9 l. of 6 N HCl with vigorous stirring. The chloroform layer was separated and washed with saturated $NaHCO_3$ and aqueous NaBr, and then dried over $MgSO_4$. Removal of solvent on a steam bath and then on a rotary evaporator at 93 °C (20 Torr) left 171 g of a clear orange residual liquid. Gas chromatography of the neat liquid at 143 °C showed that only **8** and **9** were present in a ratio of 87:13. The hydroxy acetate eluted first from the column and the CCl_4 solution spectrum of the eluent showed OH (3620, 3440 cm^{-1}) and acetate (1735, 1248 cm^{-1}). The eluent derived from the second peak showed acetate and carbonyl (1735 and 1240 cm^{-1}) but no OH absorption.

4-Acetoxycyclohexanone (10). The residual liquid derived from the above acetylation procedure (94.8 g, 0.60 mol, **8**) was dissolved in 2.4 l. of reagent grade acetone and chilled in an ice bath. Jones reagent was made by dissolving 60 g of CrO_3 in 49 ml of concentrated sulfuric acid and then diluting with 120 ml of water, giving a total volume of 184 ml. Approximately 122 ml of this reagent was placed in a vented dropping funnel and 112 ml of this volume was added to the acetone solution with vigorous mechanical stirring maintaining a reaction temperature of 10–15 °C. At this point the reaction mixture had a definite orange color and enough 2-propanol was added to turn the reaction color green again. To this mixture was added 200 g of solid $NaHCO_3$ and 30 g of Na_2CO_3 and stirring was continued for an additional 0.5 h at 15 °C. The mixture was filtered and the residue was washed thoroughly with four portions of acetone. The combined acetone filtrates were stirred over solid Na_2CO_3 and filtered. The solution was concentrated on a steam bath and then on a rotary evaporator at 30 °C until two liquid phases were clearly visible. This mixture was extracted with methylene chloride (3 × 300 ml) and the CH_2Cl_2 extracts were dried over $MgSO_4$. Removal of the solvent on a steam bath and then on a rotary evaporator at 90° (20 Torr) left 98.0 g of a clear, light yellow liquid. Gas chromatography of the neat liquid on a 4-ft silicone rubber column at 138 °C showed the presence of only two peaks which corresponded to the keto acetate **10** and the diacetate **9** in order of their retention times, respectively. The ratio of the two peaks was 87:13 and the peak corresponding to **10** was collected. The infrared spectrum showed bands at 1730 (carbonyl) and 1740 and 1240 cm^{-1} (acetoxyl); NMR τ 4.86 (distorted quartet, 1 H), 7.40–8.20 (multiplet, 11 H), 7.98 (sharp singlet, acetoxyl 3 H). A 2,4-DNP derivative was prepared from the ketone, mp 184–186 °C (lit.[16] 183 °C).

Preparation of Enamine 11. To the residual liquid from the above oxidation (85 g, 0.54 mol, of actual **10**) in 2 l. of reagent grade benzene was added 81 g (0.93 mol) of morpholine and the solution was refluxed with continuous separation of water through a Dean-Stark trap for 40 h. The solvent was removed on a rotary evaporator and the residual orange oil was distilled at 0.03 Torr. With steam being sent through the condenser the diacetate **9** was distilled at 75–97 °C. A total of 95 g of distillate was collected at 97–110 °C and 0.02 Torr. Gas chromatography showed that the diacetate was completely removed during this distillation. The ir spectrum of **11** (neat) showed bands at 3070 (C=CH), 2960, 2860, 2815, 1735, 1650, 1375, and 1250 cm^{-1}; NMR τ 5.15 (m, 1 H), 5.59 (m, 1 H), 6.38 and 7.20 (both centers of an A^2B^2 pattern, 4 H), 7.5–8.5 (m, 7 H).

Preparation of 2-Keto-7-acetoxybicyclo[3.3.1]nonan-9-one (14). To a refluxing solution of 95 ml of the above enamine **11** in 870 ml of dry benzene was added, over a period of 2 h with stirring, a solution of 42 ml of acryloyl chloride in 435 ml of benzene. Refluxing was continued for 18 h with sporadic magnetic stirring due to the fact that the brittle salt intermediate adhered to the bottom of the flask quite tenaciously. After cooling, the supernatant liquid was decanted, the residue was thoroughly washed four times with reagent grade dry benzene, and the solvent was removed under reduced pressure (20 Torr and then 0.2 Torr). Hydrolysis of the residue was accomplished by the addition of 1.1 l. of ice water and stirring was continued for 3.5 h at 0–2 °C. Solid sodium bromide (100 g) was then added to the mixture and it was extracted with methylene chloride (6 × 500 ml). After drying ($MgSO_4$) the solvent was removed on a steam bath and then on a rotary evaporator at 80 °C, leaving 87 g of a dark brown, viscous residual liquid. Distillation gave 52 g of **14**, bp 110–120 °C (0.5 Torr). The ir spectrum of **14** showed both ketone and acetoxyl absorptions at 1748, 1718, and 1240 cm^{-1}; NMR τ 4.5–5.1 (m, 1 H), 6.8–8.2 (m, 13 H).

2,7,9-Triacetoxybicyclo[3.3.1]nonane (16). The dione acetate **14** (30.2 g, 0.144 mol) in 600 ml of THF was added, with stirring under a nitrogen atmosphere at room temperature, to a suspension of 8.9 g (0.24 mol) of $LiAlH_4$ in 500 ml of THF. The temperature rose to 45 °C during addition and the color of the deep gray solid lightened considerably as the addition was continued. The solution was then refluxed with stirring under nitrogen for 18 h and after cooling 25 ml of ethyl acetate dissolved in 25 ml of THF was added to the mixture. Refluxing was then continued for 1 h. After cooling to 40 °C, 40 ml of water was added and the mixture was stirred for 35 min. This was followed by the addition of 30 ml of 15% NaOH solution with 50 min of stirring. An additional 20 ml of water was added and stirring was continued for 15 min. The resulting off-white granular precipitate was removed by filtration and washed with hot THF. Removal of solvent on a steam bath and then on the rotary evaporator at 100 °C (20 Torr) afforded 26.8 g of a light tan, waxy solid. The solid was further dried at 1 Torr and 100 °C with only insignificant weight loss. This solid was then dissolved in 122 ml of pyridine and 142 ml of acetic anhydride and the resulting solution was stirred at 63–65 °C for 18 h. After cooling, 500 ml of methylene chloride was added and the solution was acidified by the addition of 680 ml of 6 N HCl with stirring at ice bath temperatures. The aqueous layer was extracted with 200 ml of methylene chloride and the combined extracts were washed three times with 5% NaOH and once with brine. The solution was dried

($MgSO_4$) and concentrated on a steam bath and then on a rotary evaporator at 100° (20 Torr), giving 37.3 g (87%) of a honey-colored syrup (**16**). The ir spectrum of **16** (neat) showed acetate absorptions at 1735 and 1250 cm^{-1}; NMR τ 5.02 (m, 3 H), 7.5–8.5 (m, 19 H) (sharp singlet at 8.01). Gas chromatography of an acetone solution of the syrup revealed only trace quantities of lower molecular weight impurities.

Liquid Phase Pyrolysis of Triacetate 16. The above triacetate **16** (15.2 g, 0.051 mol) was placed in a 19/22 Pyrex test tube. Into this was set a 19/22 Pyrex air condenser which in turn supported a conventional distillation take-off apparatus. The test tube and approximately ⅔ the length of the air condenser was set into a furnace and the entire system was purged with nitrogen before heating. Distillation of a liquid was observed as the temperature of the furnace was increased from 354 to 400 °C during a 6-min period. As the temperature was increased from 400 to 470 °C during a 20-min period foaming and distillation occurred simultaneously. During a 33-min. period as the temperature was increased from 470 to 512 °C smooth distillation gave rise to a yellowish distillate which comprised the main bulk of the distillate. The distillate was dissolved in ether and the upper portions of the distillation apparatus were rinsed down with ether. The combined ethereal solution was washed with brine and 5% NaOH. Drying ($MgSO_4$) and removal of the solvent on the steam bath and then on the rotary evaporator gave rise to 10.1 g (84%) of **17**, a pale yellow residual liquid which showed bands for olefinic and acetoxyl functions at 3040 (m), 1740 (br), 1650 (w), and 1250 cm^{-1} (br). Analysis of the liquid by gas chromatography at 168 °C followed by programming at 5 °C/ min up to 235 °C showed the product ratio to be 76% the diacetoxy olefin **17**, 16% the acetoxydiene **18** and 6% the unchanged triacetate **16**. An NMR spectrum of **17** was obtained after collection from the column: τ 3.9–5.4 (2 multiplets, 2 olefinic H and 2 *O*-acetoxyl H), 7.2–8.6 (series of multiplets with a sharp singlet at 8.02, 14 H).

Pyrolysis of 17. Preparation of 9-Acetoxybicyclo[3.3.1]nona-2,6- (and 2,7-) diene (18). The neat diacetate **17** (9.8 g, 0.042 mol) was added, under a stream of nitrogen at a rate of 12 drops/min, to a 13-in. column of glass beads contained in a 24-in. 24/40 Pyrex tube. The tube was preheated at 530 °C by means of a furnace and its bottom was set into a trap which was almost entirely submerged in an ice bath. A brownish-black liquid collected in the trap, and after addition was complete, the hot column was washed down dropwise with benzene. After cooling, the column was thoroughly washed down with ether. The resulting ethereal benzene solution was washed with brine and 5% NaOH, dried ($MgSO_4$), and concentrated on the steam bath and then on a rotary evaporator at 80 °C, yielding 5.1 g of a brown liquid. The liquid was distilled giving dienyl acetate **18**, 3.2 g (68%), bp 80–110 °C (12 Torr). The bulk of the fraction was contaminated by only trace quantities of other compounds. Collection of the product from the column gave a sample which displayed an ir spectrum that showed characteristic absorptions for olefinic and acetoxyl moieties at 3040 (m), 1730 (s), 1370 (m), 1250 (s, br), and 1040 cm^{-1} (s, out of plane olefinic C–H mode); NMR τ 4.45 (m, 4 H), 5.18 (m, 1 H), 7.0–8.5 (m, 9 H) (sharp singlet at 8.05).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.83; H, 7.89.

Oxymercuration–Demercuration of Dienyl Acetate 18. A mixture of 1.0 g of 9-acetoxybicyclo[3.3.1]nona-2,6(7)-diene (**18**) and 3 g of mercuric acetate in 12 ml of tetrahydrofuran and 12 ml of water was stirred for 24 h at room temperature. To this was added 24 ml of tetrahydrofuran and 24 ml of 0.5 M sodium borohydride solution in 15% sodium hydroxide. Stirring was continued for 3 h followed by addition of 12 g of sodium chloride. The solution was allowed to stand overnight. The solution was filtered through glass wool and the residue washed with ether. The aqueous layer was separated and extracted with five 20-ml portions of ether. The organic layers were combined, dried over magnesium sulfate, and concentrated. Gas chromatographic analysis showed three products: **21** (15%), **19** (40%), and **20** (45%). The 2-oxaadamantan-6-ol (**19**) was isolated by column chromatography on an alumina column, 0.24 g (24%), mp 254.0–257.0 °C. Yields of other runs varied between 16 and 30%.

Anal. Calcd for $C_9H_{14}O_2$ (**19**): C, 70.10; H, 9.15. Found: C, 70.18; H, 9.14.

2-Oxaadamantan-6-one (22). Jones reagent, prepared from 18 g of chromium trioxide, 25 ml of water, and 10 ml of concentrated sulfuric acid, was added dropwise to 0.42 g of the above oxaadamantanol **19** in 25 ml of acetone at 0 °C until a light orange color appeared through the green precipitate. This was stirred for 15 min to ensure that the orange color remained. After 1.5 g of sodium bicarbonate and 0.3 g of sodium carbonate were added, the stirring was continued for 0.5 h. The solids were removed by filtration and the solvent removed on the rotary evaporator. The product was dissolved in ether and dried over magnesium sulfate. Removal of the solvent yielded 0.4 g (95%) of the oxaadamantanone **22**. Analysis by gas chromatography on silicon oil 710 and Carbowax 20M columns at 200 °C showed this to be about 98% pure. Infrared spectrum showed a triplet between 1700 and 1730 cm^{-1} indicating C=O stretching.

Anal. Calcd for $C_9H_{12}O_2$ (**22**): C, 71.03; H, 7.95. Found: C, 70.75; H, 7.89.

2-Oxa-6-adamantanamine Hydrochloride (23). 2-Oxa-6-adamantanone (**22**, 0.4 g) was dissolved in 30 ml of 95% ethanol saturated with ammonia. This was hydrogenated in a Parr hydrogenation apparatus with 0.3 g of 10% palladium on carbon and 45 psi hydrogen at 50–55 °C for 24 h. The solution was cooled and filtered to remove the catalyst. The solvent was removed, leaving an oil. The oil was dissolved in ether with a minimum amount of absolute ethanol. Dry HCl gas was bubbled through the solution which was cooled overnight and filtered. Crystals were vacuum sublimed at 175 °C, then recrystallized from ethanol–ether, giving 0.28 g (70%) of **23**, mp 375–380 °C.

Mass spectrum of **23** had peaks at *m/e* 153 (M − HCl), 152, 136 (M − NH_4Cl), 92, 70, and 56 (base peak).

Anal. Calcd for $C_9H_{16}ONCl$: C, 56.87; H, 8.57. Found: C, 56.93; H, 8.57.

2-Oxa-6-adamantanecarboxylic Acid (26). Methylmethoxytriphenylphosphonium bromide (2.5 g)[24] was added slowly to a 100-ml three-neck flask containing 5.6 ml of 1.26 M *n*-butyllithium and 30 ml of anhydrous ether at −10 to −15 °C under a nitrogen atmosphere while stirring. Stirring was continued at −10 to −15 °C for 1 h. While stirring the suspension looked orange to brown. When the suspended material was allowed to settle, the solution above it was scarlet red. To this, 0.15 g of the oxaadamantanone **22** in 10 ml of ether was added dropwise with stirring under nitrogen atmosphere at −10 to −15 °C. Stirring was continued overnight at room temperature. Anhydrous zinc chloride was added until the red color disappeared. This enol ether **24** was stirred for 1 h followed by acidification with perchloric acid (60.5%). After removal of the solvent, the residue containing the aldehyde **25** was dissolved in reagent acetone and oxidized with Jones reagent. The solvent was removed and 75 ml of water was added. This was extracted with five 20-ml portions of ether. The organic layer was extracted with five 20-ml portions of 5% sodium hydroxide solution. The alkaline phase was acidified with 37% hydrochloric acid, cooled, and extracted with five 20-ml portions of ether. The ethereal phase containing the acid **26**, was dried over magnesium sulfate and concentrated. The crystals, formed upon cooling in a refrigerator, were washed with pentane and sublimed at 125 °C at 2 Torr, yielding 0.037 g (20%) of **26**. Infrared spectrum in chloroform of the enol ether **24** showed an absorbance at 1690 cm^{-1} characteristic of an enol ether. The aldehyde **25** showed the characteristic peaks at 2860, 2720, and 1720 cm^{-1}. The acid **26** displayed absorption at 3515, 3300–2500, and 1700 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.90; H, 7.84.

Acknowledgments. We wish to thank Dr. Kenneth Rinehart for the mass spectrum.

Registry No.—**7**, 556-48-9; **8**, 58512-50-8; **9**, 19843-75-5; **10**, 41043-88-3; **11**, 57438-52-5; **14**, 58512-51-9; **16**, 58512-52-0; **17**, 58512-53-1; **18** (2,7-diene), 58512-54-2; **18** (2,6-diene), 58526-81-1; **19**, 58512-55-3; **22**, 58512-56-4; **23**, 58512-57-5; **24**, 58512-58-6; **25**, 58512-59-7; **26**, 58512-60-0; acetyl chloride, 75-36-5; morpholine, 110-91-8; acryloyl chloride, 814-68-6; ethyl acetate, 141-78-6; mercuric acetate, 1600-27-7; methylmethoxytriphenylphosphonium bromide, 33670-32-5.

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(23) Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 grating spectrophotometer in $CHCl_3$, CCl_4, or CS_2. A Varian A-60 spectrophotometer was used to record NMR spectra in CCl_4 using tetramethylsilane as an internal standard. Gas chromatographic analyses were made on a Hewlett-Packard 720 thermal conductivity gas chromatograph. Most products were determined on a 4 ft × 0.25 in. silicone rubber column on Chromosorb W. Helium flow rates of 30–40 ml/min were found optimal. Elemental analyses were carried out by Geller Laboratories, Saddle River, N.J.
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Reactions of Dicarbonyl Compounds with Dimethyl β-Ketoglutarate. 2. Simple Synthesis of Compounds of the [10.3.3]- and [6.3.3]Propellane Series[1]

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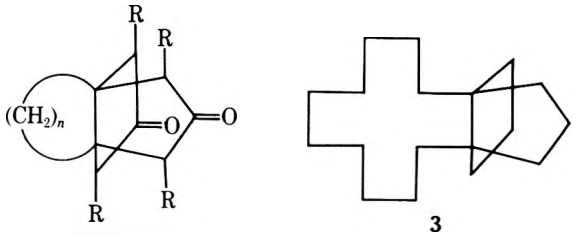
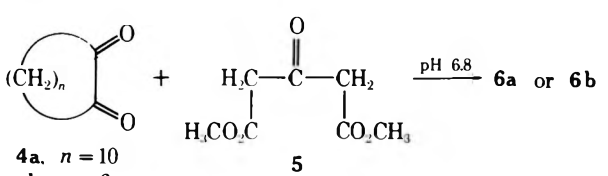
Reaction of cyclododecane-1,2-dione (**4a**) or cyclooctane-1,2-dione (**4b**) with dimethyl β-ketoglutarate (**5**) at room temperature in aqueous buffer (pH 6.8) provided good yields of tetramethyl[10.3.3]propellane-14,17-dione 13,15,16,18-tetracarboxylate (**6a**) and tetramethyl[6.3.3]propellane-10,13-dione 9,11,12,14-tetracarboxylate (**6b**), respectively. Hydrolysis and decarboxylation of **6a** and **6b** furnished the propellanediones **7a** and **7b**. The dione **7a** was converted to [10.3.3]propellane by Wolff–Kishner reduction while Clemmensen reduction of the propellanediones yielded the cyclic substituted bisnoradamantyl alcohols **11** and **12**.

Chemistry of propellanes has been given much attention in recent years.[2] In particular, a large effort has been spent upon the synthesis of propellanes containing small rings and upon the study of the bonding character of their central bond.[3] On the other hand, no propellanes with medium or large rings ($n > 6$) seem to have been prepared, presumably because of difficulties in synthesizing such compounds. However, the approach used by Weiss and Edwards[4] for the synthesis of diketo derivatives of [4.3.3]- (**1**) and [3.3.3]propellane (**2**) through reaction of cyclohexane-1,2-dione and cyclopentane-1,2-dione, respectively, with dimethyl β-ketoglutarate seemed to be capable of extension to medium-ring 1,2-diketones. This proved indeed to be the case. We wish to report here on the synthesis and properties of several compounds of the [10.3.3]- and [6.3.3]propellane series, including the parent hydrocarbon (**3**) of the former.[5]

Scheme I



1, $n = 4$; R = H
2, $n = 3$; R = H
6a, $n = 10$; R = CO_2CH_3
6b, $n = 6$; R = CO_2CH_3
7a, $n = 10$; R = H
7b, $n = 6$; R = H

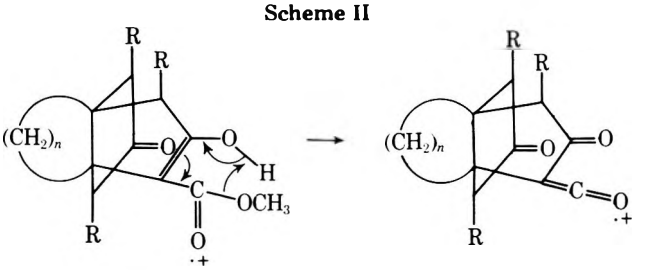


4a, $n = 10$
b, $n = 6$

5

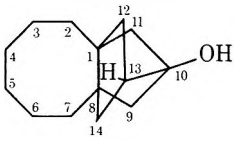
Reaction of 1 mol of cyclododecane-1,2-dione (**4a**)[6] with 2 mol of dimethyl β-ketoglutarate (**5**) in a mixture of methanol and citrate–phosphate buffer (pH 6.8) for 24 h at room temperature gave a precipitate (94%) of tetramethyl[10.3.3]propellane-14,17-dione 13,15,16,18-tetracarboxylate (**6a**), mp 156.5–158 °C (from methanol); high-resolution mass spectrum, calcd for $C_{26}H_{36}O_{10}$, 508.2308; found, 508.2300. This product of 1:2 stoichiometry was homogenous on TLC with several solvent systems; only one of the several possible stereoisomers seems to have been obtained. Structure **6a** is consistent with ir, NMR, and mass spectral data. Three successive losses of 32 units (CH_3OH) were observed from the parent ion in the mass spectrum of **6a**. This can be formulated to occur as illustrated in Scheme II to generate ketene intermediates. Similar fragmentations have been reported by

Scheme II



6a

Table I. ^{13}C Chemical Shifts for Tetracyclo[6.3.3.0.0^{10,13}]tetradecan-10-ol (11)



11

Types of carbon atoms	Chemical shift, ppm	Types of carbon atoms	Chemical shift, ppm
3 + 6	26.19[a]	13	49.63
4 + 5	27.76	11 + 9	51.30
2 + 7	28.94	1 + 8	57.10
12 + 14	44.50	10	82.11

[a] Measured from Me_4Si standard.

Biemann[7] with *cis*-crotonic acid methyl ester and are observed quite consistently in our β-keto ester derivatives. A fourth loss of 32 units was also observed but it was of very low intensity.

The tetramethyl tetracarboxylate derivative (**6a**) was hydrolyzed and decarboxylated in refluxing 6 N hydrochloric acid to furnish an oil in 90% yield which crystallized from methanol, mp 53–55 °C (CH_3OH). Spectral data unambiguously support structure **7a** for this white solid. The alicyclic protons of the 12-membered ring appeared as a singlet at δ 1.40 (20 H) in the NMR spectrum, while the cyclopentanone protons were observed as two singlets at δ 2.36 (4 H) and 2.45 (4 H), respectively. The presence of a strong band at 1741 cm^{-1} in the ir and the absence of signals from the methyl ester functions in the NMR further substantiated the structural assignment.

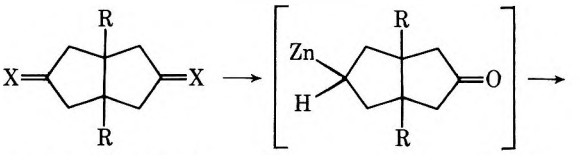
Treatment of [10.3.3]propellane-14,17-dione (**7a**) with hydrazine and base[8] furnished [10.3.3]propellane (**3**) in 54% yield. The compound was crystallized from ether, mp 33–35 °C (sublimes at 750 mmHg); high-resolution mass spectrum calcd for $C_{18}H_{32}$, 248.2504; found, 248.2499. The ir spectrum of this compound lacked carbonyl or hydroxyl bands. Two singlets (12 H and 20 H) observed in the NMR at δ 1.51 and 1.38 can be attributed to the cyclopentane and cyclododecane protons, respectively. The cyclopentane protons are somewhat deshielded compared to the cyclododecane protons because of strain in the five-membered rings.[9] A mixture of cyclopentane and cyclododecane furnished an NMR spectrum identical with that of **3**.

Reaction of cyclooctane-1,2-dione (**4b**) and **5** under conditions similar to those described above provided tetramethyl[6.3.3]propellane-10,13-dione tetracarboxylate (**6b**) in good yield. Hydrolysis with 6 N hydrochloric acid and a cosolvent (acetic acid) yielded an oil which was crystallized from methanol to furnish [6.3.3]propellane-10,13-dione (**7b**) in 85% yield, mp 80–82 °C (from CH_3OH). The similarity between the physical and spectral properties of compounds **7a** and **7b** confirmed the structural assignment of [6.3.3]propellane-10,13-dione as **7b.**

Several attempts to reduce the [6.3.3]propellane-10,13-dione (**7b**) to the parent hydrocarbon by Wolff–Kishner reduction[8] were made. None of these attempts were successful. Only traces of the oxygen-free propellane were observed and the majority of the material isolated was dimeric (see Experimental Section).

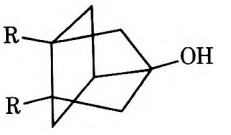
Because Wolff–Kishner reduction did not prove successful in the [6.3.3] system, it was hoped that Clemmensen reduction of the carbonyl functions would yield the parent hydrocarbon. Borden and co-workers[10] had converted 1,5-dimethylbicyclo[3.3.0]octane-3,7-dione (**8**) into 1,5-dimethylbicyclo[3.3.0]octane (**9**) by zinc amalgam reduction in aqueous solution. In addition, a small amount of the bisnoradamantyl

Scheme III

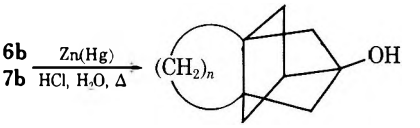


8, R = CH_3; X = O
9, R = CH_3; X = H_2
14, R = H; X = O

13



10, R = CH_3
15, R = H



11, $n = 6$
12, $n = 10$

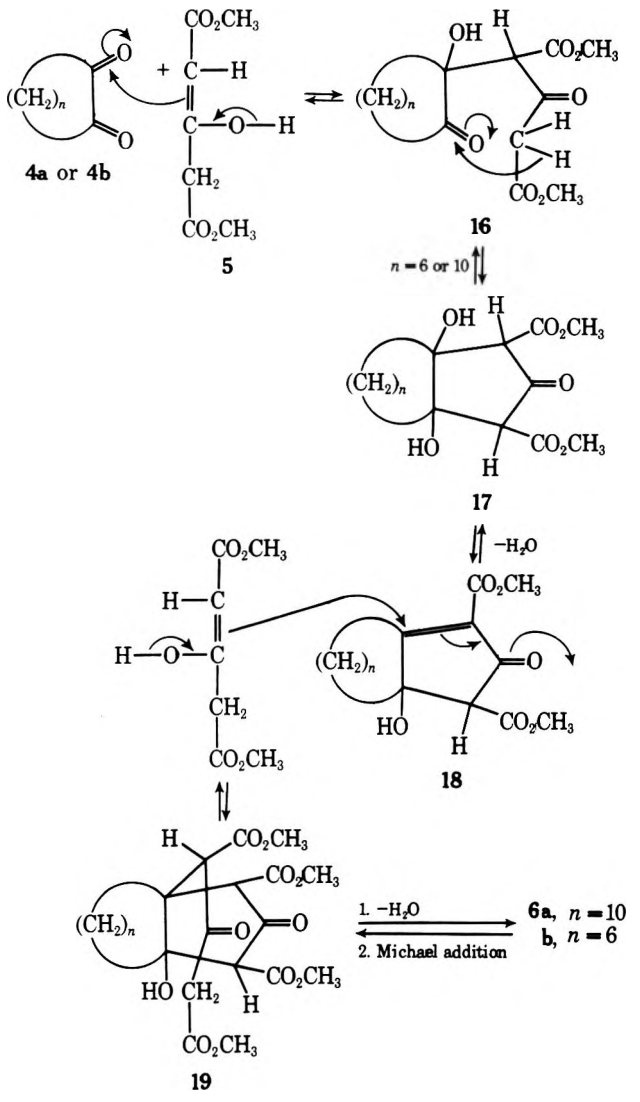
derivative 3,7-dimethyltricyclo[3.3.0.0^{3,7}]octan-1-ol (**10**) was isolated; the acetate of **10** was the major product on reduction in acetic anhydride. Consequently, this reduction was expected to be straightforward; however, when [6.3.3]propellane-10,13-dione was reduced with Zn(Hg) in aqueous HCl at reflux, a crystalline compound (mp 87–88 °C) containing one oxygen atom was isolated in 69% yield (high-resolution mass spectrum, calcd for $C_{14}H_{22}O$, 206.1670; found 206.1670). The compound was nonketonic but contained a hydroxy group (ir). Since the NMR spectrum lacked signals from methylene protons or methine protons next to oxygen the compound appeared to contain a tertiary hydroxy function analogous to compound **10** reported by Borden.[10] The structure which best fits the spectroscopic evidence is tetracyclo[6.3.3.0.0^{10,13}]tetradecan-10-ol (**11**). This structure is strongly supported by ^{13}C NMR (see Table I). The oxygen-substituted tertiary carbon (C-10) appeared at lowest field (82.11 ppm), clearly distinct from the other carbon atoms, while carbon atom 13 was observed at 49.63 ppm. The remaining 12 carbon atoms appeared as six singlets. Each of these singlets represented two carbon atoms because of the symmetry of this part of the molecule as depicted in Table I.[11] When [10.3.3]propellane-14,17-dione was allowed to react under the same conditions, a 70% yield of tetracyclo[10.3.3.0.0^{14,17}]octadecan-14-ol (**12**), mp 142–143 °C (from methanol) was realized. The structure was confirmed by comparison with data collected on **11**. In addition, the tertiary proton present on C-17 of the tetracyclooctadecanol **12** was observed as a triplet at δ 2.09 in the 220-MHz NMR spectrum. The other signals in this spectrum were also in accord with this assignment.

The reduction conditions employed in the work of Borden for conversion of **8** to **9** provided substantial amounts of 1,5-dimethylbicyclo[3.3.0]octane (**9**). We never observed any trace of the parent hydrocarbon (**3**) in our reaction. A plausible mechanism for the formation of the bridge between the two carbon atoms has been proposed;[10] the zinc-stabilized carbanion (**13**) resulting from reduction of one carbonyl function of **8** can react intramolecularly with the second carbonyl function to form the C(10–13) bridge. Our work is in agreement with this postulated mechanism but the higher temperature here may have allowed more interaction between the two carbonyls leading to substantially higher yields of the bridged tetracyclo species **11** and **12**. We then attempted to convert bicyclo[3.3.0]octane-3,7-dione (**14**) to bisnoradamantyl alcohol (**15**) at reflux, but obtained only complex mix-

tures of products, none of which appeared to be the desired alcohol **15**.

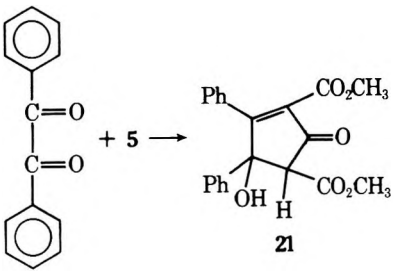
The preferential 1:2 stoichiometry observed in the reaction of 1,2-diketones and dimethyl β-ketoglutarate including **4a** and **4b** can be explained through a sequence suggested by Weiss[12] and supported by our work.[5] It is shown for the compounds described in the present paper in Scheme IV. In

Scheme IV



this sequence aldol condensation of **4a** or **4b** and **5** is assumed to give the β-hydroxy ketones **16** and **17**; the latter would lose one molecule of water to give the 4-hydroxycyclopenten-2-one derivative (**18**). Michael addition of a second molecule of **5** would provide **19** which could then lose another molecule of water; and a second Michael reaction (intramolecularly) would generate the observed final products **6a** and **6b**.

All attempts to isolate the 1:1 intermediates **17** or **18** from the reaction at pH 6.8 have been so far unsuccessful. Even when the reaction was carried out with a 10:1 excess of the 1,2-dicarbonyl compound, the product first observed by TLC, or isolated, was the propellanedione **6a**. However, a 1:1 adduct entirely analogous to **18** has been obtained already by Japp and Lander[13] from the reaction of benzil and β-ketoglutaric acid in alcoholic KOH and we have encountered several other compounds of this type. Under the conditions used by Japp and Lander, we have obtained the 1:1 adduct (**21**) closely related to their cyclopentenolone, from benzil (**20**) and dimethyl β-ketoglutarate (**5**). The same compound was prepared independently by White.[14] When cyclododecane-1,2-dione (**4a**) was treated with **5** in alcoholic KOH two compounds were



20 **21**

observed by TLC. The less polar one of these was identified as the propellanedione **6a**. All attempts to isolate the second, more polar substance have yielded only the propellanedione **6a**. We feel that this new compound may be the 4-hydroxycyclopenten-2-one (**18**) analogous to **21**. A paper which discusses the details of this mechanism and which reports on isolation of 1:1 adducts in related systems is in preparation.[15] Reaction of **4a** and **5** in methanol with sodium methoxide also provided **6a**.

In the buffer system (pH 6.8), the rate of the Michael addition of dimethyl β-ketoglutarate to the 4-hydroxycyclopenten-2-one (**18**) seems to be faster than the formation of **18** itself; consequently, only the adducts of 1:2 stoichiometry have been isolated.

We have also investigated reaction of **4a** and **5** under anhydrous acidic conditions. When cyclododecane-1,2-dione (**4a**) and dimethyl β-ketoglutarate (**5**) were allowed to react in refluxing benzene in the presence of a small amount of *p*-toluenesulfonic acid, a colorless compound was isolated in small yield, mp 85–86 °C (from CH_3OH); high-resolution mass spectrum calcd for $C_{19}H_{26}O_5$, 334.1780; found, 334.1788. This is evidently formed from one molecule each of the reactants by elimination of two molecules of water. The NMR of this 1:1 adduct is very complex and suggests that extensive rearrangement has occurred during formation of this substance.

It appears that reaction of alicyclic α-dicarbonyl compounds with dimethyl β-ketoglutarate will in general proceed with 1:2 stoichiometry to furnish tetramethylpropellanedione tetracarboxylate derivatives in good yield, and similar results are obtained in alkaline methanol. In contrast to this, the reaction in refluxing benzene appears to give a 1:1 adduct, although some rearrangement may take place and in addition, reactions of aromatic α-diketones also yield 1:1 adducts.[16] At no time did we observe the formation of a propellanedione on reaction of benzil and dimethyl β-ketoglutarate.

Experimental Section

Microanalyses were performed (UWM) on an F & M Scientific Corp. Carbon, Hydrogen, Nitrogen Analyzer Model 185; some analyses were carried out at the National Institutes of Health, Bethesda, Md. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian T-60, HA-100, and CFT-20 spectrometers. Infrared spectra were taken on a Beckman Acculab-1 instrument, ultraviolet spectra were recorded on a Cary 17 spectrophotometer, and mass spectra were taken on a Finnigan 1015 or AEI MS902 instrument.

Analytical TLC plates used were E. Merck-Brinkmann uv active silica gel on plastic. The spray reagent was composed of 2,4-dinitrophenylhydrazine, ethanol, and sulfuric acid. The citrate–phosphate buffer (pH 6.8) was prepared by dissolving $Na_2HPO_4 \cdot 7H_2O$ (11.67 g) and citric acid (3.68 g) in water (900.00 ml).

Preparation of Cyclododecane-1,2-dione (4a) and Cyclooctane-1,2-dione (4b). The 1,2-dione **4a** was prepared by the method of Sharpless,[6] yield 50%, bp 90–94 °C (0.8 mmHg) [lit. 93–95 °C (1 mmHg)].[6] Cyclooctane-1,2-dione (**4b**) was prepared by the same method, albeit in very low yield. Higher yields of **4b** were obtained by acyloin condensation[17] followed by oxidation:[18] bp 68–69.5 °C (3 mmHg) [lit.[19,20] bp 68.8–69.5 °C (3 mmHg)].

Tetramethyl[10.3.3]propellane-14,17-dione 13,15,16,18-Tetracarboxylate (6a). Cyclododecane-1,2-dione (5.0 g, 0.025 mol) was dissolved in methanol (100 ml) and citrate–phosphate buffer (pH 6.8)

was added until the solution became turbid. A few additional drops of methanol were added to clarify the solution and dimethyl β-ketoglutarate (8.87 g, 0.050 mol) was added all in one portion. After stirring for several hours at room temperature, a white precipitate began to form. The reaction was continued for 3 days and then the mixture was filtered. A white, crystalline solid (11.9 g) was isolated by filtration in 94% yield. It was homogenous on TLC (R_f 0.39, 1:9 ethyl acetate/benzene). The product was recrystallized from methanol, mp 156.5–158 °C (unchanged on further recrystallization) and identified as **6a**: ir ($CHCl_3$) 2930 (C–H), 1728 (ester carbonyl), and 1653 cm^{-1} (enol form of β-keto ester); uv λ_{max} (CH_3OH) 246.8 nm; NMR δ ($CDCl_3$) 1.45 (20 H, broad singlet), 3.68–4.20 (14 H, six singlets of unequal intensity), 10.64 (1 H, s, enol proton), and 10.72 (1 H, s, enol proton), both enol protons D_2O exchangeable; mass spectrum M^+ *m/e* 508.2300 (calcd for $C_{26}H_{36}O_{10}$, 508.2308); *m/e* 508 (49, M^+), 490 (27.1, M − 18), 477 (79.2), 476 (100, M − 32), 446 (5.8), 444 [50.1, M − (2 × 32)], 443 (12.1), 442 (15.8), 414 (15.1), 412 [43.1, M − (3 × 32)], 410 (5.3), 404 21.5), 382 (17.8), 399 (5.5), 380 [6.0, M − (4 × 32)], and 300 (4.0).

Anal. Calcd for $C_{26}H_{36}O_{10}$: C, 61.40; H, 7.10. Found: C, 61.62; H, 7.18.

[10.3.3]Propellane-14,17-dione (7a). The tetramethylpropellanedione tetracarboxylate (**6a**, 5.1 g, 0.01 mol) was dissolved in 6 N hydrochloric acid (60 ml) and the solution was refluxed for 6 h. After extraction with chloroform (5 × 50 ml), washing of the combined organic layers with water, and drying (Na_2SO_4), the solution was evaporated under reduced pressure to yield a brown oil. The oil was taken up in hot methanol; on cooling, white crystals formed (2.5 g, 90% yield) of mp 53–55 °C: ir ($CHCl_3$) 2915 (C–H), 2850 (C–H), and 1741 cm^{-1} (cyclopentanone C=O); NMR ($CDCl_3$) δ 1.40 (20 H, s), 2.36 (4 H, s), and 2.45 (4 H, s); mass spectrum *m/e* 276 (100, M^+), 248 (89.6), 233 (18), 220 (73), 218 (31), 205 (14.5), 195 (16.6), 191 (8.3), 177 (16.6) 164 (10), 163 (20), 149 (40), 150 (14.5), 135 (56.2), 122 (67), and 121 (68.7).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.30; H, 10.10. Found: C, 78.10; H, 10.28.

[10.3.3]Propellane (3). The propellanedione **7a** (0.50 g, 0.0098 mol) and hydrazine (4.5 g of 95%) were added to a mixture of diethylene glycol and potassium hydroxide pellets (2.4 g). The reaction mixture was slowly heated to 135 °C[8] until the potassium hydroxide pellets dissolved; the solution was refluxed for 1 h. The water and excess hydrazine were distilled from the mixture (750 mmHg) until the pot temperature reached 180 °C. The viscous residue was heated for 3 h at 180 °C, cooled to room temperature, and then poured into cold water (40 ml). The aqueous solution was extracted with benzene (5 × 25 ml), and the combined extracts were washed several times with small portions of water and dried (Na_2SO_4). Partial removal of solvent provided white crystals (0.24 g, 54%) of **3** with mp 33–34 °C (sublimed) and R_f 0.64 (benzene). The spectral data were as follows: ir ($CHCl_3$) 2930 and 2860 cm^{-1} (C–H); NMR ($CDCl_3$) δ 1.38 (20 H, s, cyclododecane protons) and 1.52 (12 H, s, cyclopentane protons); mass spectrum *m/e* 248 (100, M^+), 220 (51), 205 (50), 203 (4.4), 177 (4.4), 163 (8.5), 149 (20), 135 (53.3), 122 (99), 122 (100); M^+ at *m/e* 248.2499; calcd for $C_{18}H_{32}$, 248.2504.

Tetramethyl[6.3.3]propellane-10,13-dione 9,11,12,14-Tetracarboxylate (6b). This compound was prepared from **4b** under the same conditions as the preparation of **6a** above; however, the yield (9 g) of crystalline **6b** was only 80%, mp 160–163 °C (from methanol); ir ($CHCl_3$) 2940, 2850 (C–H), 1730 (ester C=O) and 1648 cm^{-1} (enol form of β-keto ester); NMR ($CDCl_3$) δ 1.3–1.7 (12 H, broad multiplet), 3.6–4.0 (14 H, several overlapping singlets of unequal intensity, 4 OCH_3 and two nonenolized β-keto ester protons); mass spectrum M^+ at *m/e* 452.1689; calcd for $C_{22}H_{28}O_{10}$, 452.1682; low-resolution *m/e* 452 (11.4, M^+), 420 (83), 388 (100), 360 (41), 356 (65.8), 329 (51.5), 328 (54.2), 319 (34), 297 (57.2), 296 (29), 287 (42), 278 (21), 272 (32), 246 (67), 229 (56), 214 (95), 202 (44); uv λ_{max} (CH_3OH) 244 nm.

Anal. Calcd for $C_{22}H_{28}O_{10}$: C, 58.40; H, 6.20. Found: C, 58.13; H, 6.50.

[6.3.3]Propellane-10,13-dione (7b). To a solution of glacial acetic acid (55 ml), concentrated hydrochloric acid (40 ml), and water (20 ml), tetramethyl[6.3.3]propellane-10,13-dione 9,11,12,14-tetracarboxylate (4.5 g, 0.010 mol) was added and the resultant mixture was refluxed for 10 h. A portion of the excess acid was removed under reduced pressure and the residue made alkaline with sodium bicarbonate. The basic solution was next extracted with chloroform (10 × 50 ml) and the extracts were combined and dried (Na_2SO_4). Evaporation of solvent furnished an oil (1.9 g, 85%) which on dissolution in a small amount of hot methanol provided white crystals of **7b**, mp 80–82 °C (R_f 0.15 in 20% ethyl acetate/benzene): ir ($CHCl_3$) 1740 cm^{-1} (cyclopentanone C=O); NMR ($CDCl_3$) δ 1.40–1.93 (12 H, broad singlet), 2.35 (4 H, s, cyclopentanone protons), and 2.38 (4 H, s, cyclopentanone protons); mass spectrum *m/e* 220 (100, M^+), 192 (12.5, M − 28), 188 (43.8), 164 [100, M − (2 × 28)], 149 (52.5), 135 (50), 136 (52.5), 123 (50), 121 (52.5), 109 (88), 108 (80), and 107 (75).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.40; H, 9.10. Found: C, 76.45; H, 9.35.

Attempted Reduction of [6.3.3]Propellane-10,13-dione (7b). A. A mixture of **7b** (0.50 g, 0.0022 mol), hydrazine (1.5 g of 95%), diethylene glycol (9.2 ml), and potassium hydroxide pellets (1.2 g) was heated slowly to 146 °C. After the liquid had refluxed (dry ice–acetone cold finger condenser) at this temperature for 1 h, the water and excess hydrazine were distilled from the solution until the pot temperature reached 200 °C. The viscous residue was heated at 200 °C another 3 h, cooled to room temperature, and poured into water (20 ml). The solution was extracted with benzene (8 × 25 ml). The combined extracts were washed several times with small portions of water and the organic layer was dried (Na_2SO_4). Evaporation of solvent afforded an oil (0.2 g, R_f 0.655, benzene): ir ($CHCl_3$) 2930 and 2870 cm^{-1} (C–H); mass spectrum *m/e* 380 (29.9, M_1+), 376 (38.4, M_2+), 361 (6.0), 351 (6), 337 (100), 295 (7), 279 (8.5), 232 (19.6), 229 (15), 215 (13), 204 (14.5), 203 (14.5), 192 (2.0), 189 (37.6), 187 (20.5), 173 (13), and 167 (32). This appears to be composed of two dimeric compounds M^+ at *m/e* 380 and M^+ at *m/e* 376.

B. When the reaction was repeated using excess hydrazine (5.5 g of 95%), diethylene glycol (200 ml), and potassium hydroxide pellets (3 g), an oil (0.2 g) was isolated which had R_f 0.47 (benzene); ir ($CHCl_3$) 2930 and 2860 cm^{-1} (C–H); mass spectrum *m/e* 376 (100, M^+), 361 (12.5), 347 (15), 334 (30), 319 (10), 276 (74), 248 (78), 239 (16), 233 (25), 229 (29), and 220 (59). None of the [6.3.3]propellane was observed in this experiment.

Tetracyclo[10.3.3.0.0^{14,17}]octadecan-14-ol (12). A mixture of zinc (2 g), mercuric chloride (0.2 g), concentrated hydrochloric acid (0.1 ml), and water (2 ml) was stirred for 5 min. The aqueous layer was then decanted to furnish the zinc amalgam. Water (1 ml), hydrochloric acid (4 ml of concentrated), glacial acetic acid (2 ml), and **7a** (1.0 g, 0.0036 mol) were added to the amalgam and the resulting mixture was refluxed for 20 h.[21] The solution was next cooled, decanted into water (30 ml), and refrigerated for 2 days. A white, crystalline solid (0.66 g, 70%) formed which was filtered off, mp 142–143 °C (from methanol). The spectral data are in accord with structure **12**: ir ($CHCl_3$) 3460 (OH) and 2490 cm^{-1} (C–H); 220-MHz NMR ($CDCl_3$) δ 1.43 (20 H, m), 1.64 (4 H, m), 1.76 (4 H, m), and 2.09 (1 H, t); mass spectrum M^+ at *m/e* 262.2295; calcd for $C_{18}H_{30}O$, 262.2296; *m/e* 262 (100, M^+), 233 (83.3), 220 (75), 244 (20), 207 (50), 191 (16.6), 177 (25), 163 (50), 151 (45), 149 (66), 135 (100). Solvent of crystallization was tightly bound in the crystals and precluded exact analysis.

Tetracyclo[6.3.3.0.0^{10,13}]tetradecan-10-ol (11). The same reduction procedure was employed to convert **7b** to **11**.[21] It furnished a 69% yield (0.52 g) of the alcohol **11**: mp 87–88 °C (benzene); R_f 0.3 (methylene chloride); ir ($CHCl_3$) 3440 (OH) and 2925 cm^{-1} (C–H); NMR ($CDCl_3$) δ 1.48–1.50 (20 H, two overlapping singlets) and 1.78–2.2 (1 H, broad multiplet); mass spectrum *m/e* 206 (43.7), 177 (62.5), 164 (73), 163 (100), 150 (25), 151 (37), 149 (75), 136 (99), 122 (69), and 121 (100); M^+ at *m/e* 206.1670; calcd for $C_{14}H_{22}O$, 206.1670. ^{13}C data are contained in the text.

Reaction of Benzil (20) and Dimethyl β-Ketoglutarate (5) in Potassium Hydroxide/Ethanol[13] to Yield 2,5-Dicarbomethoxy-4-hydroxy-3,4-diphenylcyclopent-2-enone (21). To a solution of potassium hydroxide (0.5 g) in ethanol (125 ml of absolute), benzil (10.5 g, 0.05 mol) was added with stirring. Dimethyl β-ketoglutarate (17.4 g, 0.10 mol) was then added to the solution and the reaction stirred at room temperature. White crystals formed within several hours and were filtered from the reaction mixture after 20 h. The crystals (12.8 g, 70%) were washed with water and dried: mp 136–140 °C; ir (KBr) 3460 (OH) and 1740 cm^{-1} (ester C=O), M^+ at *m/e* 366; NMR identical with that of **21** reported by White.[14]

Reaction of Cyclododecane-1,2-dione (4a) with Dimethyl β-Ketoglutarate in Potassium Hydroxide/Methanol. Cyclododecane-1,2-dione (2.0 g, 0.010 mol) and dimethyl β-ketoglutarate (0.24 g, 0.0013 mol) were dissolved in methanol. Methanolic potassium hydroxide (0.1 g of potassium hydroxide in 20 ml of methanol) was added to the reaction and the solution was stirred continuously for several hours. A new compound, R_f 0.16 (20% ethyl acetate/benzene), was observed on TLC; however, after workup and column chromatography only the propellanedione **6a** with R_f 0.40 was isolated. No trace of the new compound (R_f 0.16) could be found after column chromatography or preparative TLC.

Reaction of Cyclododecane-1,2-dione with Dimethyl β-Ketoglutarate in Sodium Methoxide/Methanol. This reaction was carried out as outlined in the preceding experiment; however, sodium methoxide was used in place of potassium hydroxide.[22] A new com-

pound (R_f 0.70, M^+ 392) precipitated from the solution while the propellanedione **6a** was observed by TLC of the mother liquor. This substance (R_f 0.70) was the product of reaction of one molecule of the 1,2-dione (**4a**) with another molecule of **4a** since it was also obtained by carrying out the same reaction in the absence of dimethyl β-ketoglutarate. No 1:1 adduct of **4a** and **5** could be found.

Acid-Catalyzed Reaction of Cyclododecane-1,2-dione and Dimethyl β-Ketoglutarate in Refluxing Benzene. Cyclododecane-1,2-dione (3.0 g, 0.015 mol), dimethyl β-ketoglutarate (**5**, 3.2 g, 0.018 mol), and *p*-toluenesulfonic acid (200 mg) were dissolved in benzene (70 ml). The solution was refluxed and water (0.4 ml) was removed by means of a Dean-Stark trap. Evaporation of the benzene afforded an oil (6 g) which was found to be a mixture of starting material and a *new compound* (R_f 0.42 in 10% ethyl acetate/benzene). The oil was chromatographed on silica gel which furnished a small quantity of the new compound (0.3 g, 6% yield). This substance was crystallized from methanol to provide white crystals: mp 85–86 °C; ir (CCl_4) 2940 and 2870 (C–H), 1740, 1715 with a shoulder at 1700 cm^{-1} (saturated and unsaturated ester functions); NMR ($CDCl_3$) δ 1.21–1.91 (12 H, broad multiplet), 2.2 (q, 2 H), 2.8 (t, 2 H), 3.62–3.7 (6 H, two overlapping singlets), 3.95 (s, 2 H), and 6.2 (m, 2 H); mass spectrum M^+ at *m/e* 334.1788; calcd for $C_{19}H_{26}O_5$, 334.1773; *m/e* 334 (100), 306 (14), 302 (57), 291 (816), 276 (20), 275 (100), 274 (40), 270 (1.4), 251 (14), 246)10.7), 245 (15), 231 (15), 228 (16), 219 (23), 218 (24), 205 (34), 203 (34), 192 (35), 191 (61.3), 189 (57), 173 (30), 159 (51), 149 (54), 145 (35), and 131 (65).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.30; H, 7.8. Found: C, 68.00; H, 8.02. The structure of this compound is still undetermined.

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Registry No.—**3**, 58602-52-1; **4a**, 3008-41-1; **4b**, 3008-37-5; **5**, 1830-54-2; **6a**, 58602-53-2; **6b**, 58602-54-3; **7a**, 58602-55-4; **7b**, 58602-56-5; **11**, 58602-57-6; **12**, 58602-58-7; **20**, 134-81-6; **21**, 16691-78-4.

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(22) Mr. Steven Bertz (Harvard University) has carried out this reaction on a related compound (unpublished results).

Photochemical Reactivity of Some Bridgehead Phenyl Ketones[1]

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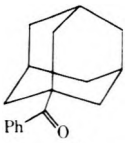
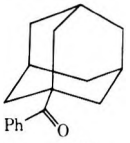
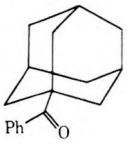
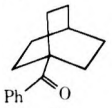
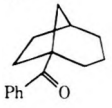
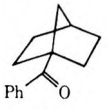
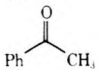
The photochemistry of several bridgehead phenyl ketones has been investigated. Bicyclo[2.2.2]octyl, 1-adamantyl, and 1- and 3-homoadamantyl phenyl ketones undergo efficient photochemical α-cleavage in benzene solution, whereas bicyclo[3.2.1]octyl and bicyclo[2.2.1]heptyl phenyl ketones do not. The rates for α-cleavage of ketones **1–4** are dependent upon bi- and tricycloalkane structure in a manner similar to that previously reported for the thermolysis of bridgehead peresters. The rate constant for α-cleavage is accelerated for 1- or 3-homoadamantyl vs. *tert*-butyl, but retarded by the smaller bicyclic ring systems. The kinetic results are indicative of an early transition state with polar character for photochemical α-cleavage. Quantum yields for product formation are larger for the bridgehead ketones than for pivalophenone owing to a decreased cage effect. The photoreduction of these ketones has also been investigated.

Reliable prediction of reactivity of an entire class of molecules is one of the ultimate goals of the investigation of reaction mechanisms. We have studied the reactivity of phenyl ketones toward photochemical α-cleavage (eq 1) with the

$$\mathrm{PhC(=O)R} \xrightarrow{h\nu} \mathrm{PhC(=O)\cdot} + \cdot\mathrm{R} \qquad (1)$$

above goal in mind.[3–5] We have established that the stability of the product free radicals does not correlate with photochemical reactivity. For example, pivalophenone (R = *tert*-butyl) is an order of magnitude more reactive than deoxybenzoin (R = benzyl).[3] We have also found that α substituents capable of stabilizing an adjacent positive charge are far more effective in accelerating α-cleavage than are substituents ca-

Table I. Absorption and Room-Temperature Phosphorescence Data for Bridgehead Ketones

Ketone		λ_{max}[a]	(ϵ)	Φ_P[b]	τ, μs[c]	τ_R, ms
1		316	(137)	$<10^{-5}$		
2		316	(129)	$<10^{-5}$		
3		317	(137)	$\sim 5 \times 10^{-5}$		5.9[d]
4		316	(140)	6.4×10^{-4}	5.4	8.3
5		319	(104)	2.8×10^{-4}	2.0	7.1
6		318	(106)	6.1×10^{-3}	30	5.0
7		317	(130)			
8		316	(63)	1.5×10^{-2}	56	3.7

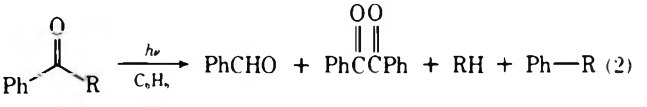
[a] Long wavelength absorption maximum in ethanol solution, 23 °C. [b] Phosphorescence quantum yield in degassed carbon tetrachloride, 23 °C. [c] Lifetime of room-temperature emission. [d] Calculated using the lifetime determined by Stern–Volmer product quenching (Table II).

pable of stabilizing free-radical centers.[4,5] In order to obtain further information about the photochemical α-cleavage process, the reactivity of six bridgehead bi- and tricycloalkyl phenyl ketones has been investigated. Studies of bridgehead reactivities have provided useful information about the mechanisms of carbonium ion[6] and free-radical[7,8] reactions. However, there are no previous reports of photochemical reactivities of bridgehead substrates.

Results

The bridgehead ketones **1–6** were synthesized via the reaction of the known carboxylic acids with phenyllithium or diphenylcadmium. Ketones **1–6** have n, π^* absorption and low-temperature emission spectra (E_T = 72 ± 1 kcal/mol) similar to that of pivalophenone (**7**, Table I) and have intersystem crossing quantum yields of 1.0 ± 0.05, as determined by comparison with benzophenone.[9] Room temperature phosphorescence was observed for ketones **3–6** in highly degassed, purified carbon tetrachloride solution. Phosphorescence quantum yields were measured by comparison to benzophenone (Φ = 0.015).[5,10] Lifetimes were determined either by single photon counting (**4** and **5**) or by signal-averaged flash kinetics (**6**).[5] The emission of ketone **3** was too weak to permit direct lifetime measurement. Radiative lifetime values for ketones **3–6** are intermediate between those for acetophenone (**8**, 3.7 ms) and benzophenone (10 ms).[5]

Irradiation of ketones **1–4** in degassed benzene results in formation of benzaldehyde, traces of benzil, bi- or tricycloalkane, and phenybi- or tricycloalkane (eq 2). These products



1, R = 3-homoadamantyl
2, R = 1-homoadamantyl
3, R = 1-adamantyl
4, R = 1-bicyclo[2.2.2]octyl
5, R = 1-bicyclo[3.2.1]octyl
6, R = 1-bicyclo[2.2.1]heptyl

are derived from the benzoyl–alkyl radical pair formed upon α-cleavage (eq 1). Ketones **5** and **6** are relatively inert to photolysis in benzene. Under conditions sufficient for >90% conversion of ketones **1** or **2**, ketone **5** is recovered ≳90% unchanged and ketone **6** is recovered quantitatively. Irradiation of **1–4** in 0.03 M dodecanethiol–benzene results in greatly increased yields of benzaldehyde, owing to efficient scavenging of benzoyl radicals.[3] Quantum yields for benzaldehyde formation (313-nm irradiation, benzophenone–benzhydrol actinometry) are given in Table II. Triplet lifetimes for ketones **1–4** were determined by the usual Stern–Volmer analysis using naphthalene as quencher both in benzene (λ >330 nm) and in 0.003 M thiol–benzene (λ 365 nm) solutions. The results obtained by the two methods are in good agreement. The lifetimes determined in benzene solution for ketone **4** are somewhat shorter than the value obtained by single photon counting in carbon tetrachloride solution (Table I). The longer lifetime is considered to be more accurate in light of the known

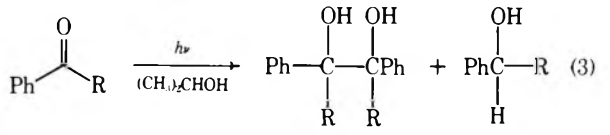
Table II. Quantum Yield and Kinetic Data for Bridgehead Ketones

Ketone	Φ^a	$k_q\tau$, M^{-1}	τ, s^d
1	0.65	24[b]	4.9×10^{-9}
		25[c]	5.0×10^{-9}
2	0.74	230[b]	4.6×10^{-8}
		280[c]	5.5×10^{-8}
3	0.68	1500[b]	2.9×10^{-7}
		600[c]	1.2×10^{-7}
4	0.13	5800[b]	1.2×10^{-6}
		6500[c]	1.3×10^{-6}
5	<0.01		
6	0		
7[e]	0.30	447	9.1×10^{-8}

[a] Quantum yield for benzaldehyde formation in degassed 0.03 M dodecanethiol–benzene solution, 313 nm irradiation. [b] Slope of linear Stern–Volmer plot (λ 365 nm). [c] Slope of linear Stern–Volmer plot (λ >330 nm). [d] Calculated assuming $k_q = 5 \times 10^9\ M^{-1}\ s^{-1}$. [e] Data from ref 12.

ability of benzene to shorten the lifetime of aromatic ketones having lifetimes longer than 1 μs.[4,11]

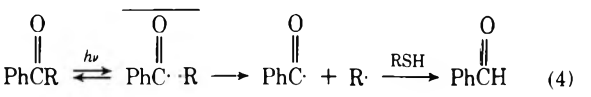
Irradiation of ketones **1–3** in 2-propanol solution results in increased yields of tricycloalkane formation (55–71% isolated yields), but none of the products expected for aryl ketone photoreduction.[12] Ketones **4** and **5** give complex mixtures of α-cleavage products along with the corresponding pinacols and carbinols (eq 3). Photoreduction is the exclusive photochemical reaction for ketone **6** in 2-propanol. Isolated yields of photoreduction products are indicated in eq 3.



4	36%	9%
5	26%	11%
6	74%	17%

Discussion

For bridgehead ketones **1–4**, the only observed primary photoprocess in benzene solution is α-cleavage (eq 1). We have previously demonstrated that quantum yields less than 1.0 for product formation result from cage recombination of the initially formed radical pair (eq 4).[13] Low concentrations of



thiol (RSH) can efficiently scavenge benzoyl radicals once they have escaped from the solvent cage in which they are formed. Quantum yields for benzaldehyde formation of 0.3–0.5 have been observed for a number of *tert*-alkyl and benzyl phenyl ketones.[3-5,12,13] Quantum yields for ketones **1–3** (Table II) are significantly higher than these values. The quantum yield for ketone **4** is 0.13, substantially lower than the values for ketones **1–3**. The lifetime of **4** is sufficiently long (5.4 μs in CCl_4) that quenching by benzene can occur.[4,11] Since the lifetime of **4** in benzene solution is approximately one-fourth as long as in carbon tetrachloride, ~75% of the excited states are quenched by benzene solvent. The resulting corrected quantum yield for ketone **4** is 0.52, nearly as large as those for ketones **1–3**. Thus we conclude that α-cleavage is the dominant decay process for ketone **4** in carbon tetrachloride solution.

The higher quantum yields for benzaldehyde formation from ketones **1–3** vs. pivalophenone ($\Phi = 0.3$) indicates that a higher percentage of benzoyl radicals escape from the solvent cage. This decreased cage effect could result from either a decreased rate of radical pair recombination or an increased rate of diffusion. The apparent rate of diffusion out of the cage could increase owing to increased mass of the alkyl radical.[14] Larger radicals may migrate over longer distances before being slowed down by the frictional resistance of the solvent and beginning their random walk leading to recombination. The failure to observe CIDNP effects for the bridgehead phenyl ketones is in accord with this explanation.[15] Alternatively, cage recombination may be slower for the bridgehead vs. acyclic radicals since one face of the bridgehead radical is protected from attack by the benzoyl radical. This explanation can be valid only if alkyl radical rotation is not significantly faster than cage recombination or diffusion. We have observed similar rates of cage recombination, diffusion, and alkyl radical rotation for the benzoyl-1-phenylethyl radical pair.[13]

The lifetimes of the bridgehead ketone n, π^* triplet states increase with decreased ring size (Tables I, II). Values of $1/\tau$ relative to that for pivalophenone are given in Table III. Since neither triplet energies nor radiative lifetimes (Table I) are dependent upon alkyl structure we assume that the variation in triplet lifetime reflects a decrease in the rate constant for α-cleavage with decreasing ring size. Only those ketones with lifetimes shorter than 1 μs undergo appreciable α-cleavage in benzene solution. The lifetime of **6** in CCl_4 is almost as long as that of acetophenone (Table I). Thus **6**, like acetophenone, would be expected to decay exclusively by radiative and nonradiative pathways to the ketone ground state. The absence of α-cleavage from ketone **5** is less readily explained. The lifetime of ketone **5** is actually shorter than that of **4**, which undergoes moderately efficient α-cleavage in benzene. In view of the apparent photochemical stability of ketone **5**, its short lifetime must be due either to a nondestructive decay pathway or to impurity quenching.

The effect of bridgehead bi- and tricycloalkane structure on reactivity for several types of homolytic and heterolytic reactions are given in Table III. Schleyer[16] has shown that a linear correlation exists between solvolysis rate constants and the calculated difference in strain energy of the bridgehead

Table III. Bridgehead Reactivities

R	PhCR[a] $1/\tau$ 22 °C	RCOO-*t*-Bu[b] k_{therm} 80 °C	R-N=N-R[c] k_{therm} 300 °C	RBr[d] solvolysis
tert-Butyl	1	1	1	1
3-Homoadamantyl	20	15.2		0.5
1-Homoadamantyl	1.8	3.5		
1-Adamantyl	0.33	2.3	4.0×10^{-4}	10^{-3}
1-Bicyclo[2.2.2]octyl	0.017	0.16	5.1×10^{-5}	10^{-6}
1-Bicyclo[3.2.1]octyl	0.045	0.082	3.7×10^{-5}	10^{-6}
1-Bicyclo[2.2.1]heptyl	0.003	0.0025	2.0×10^{-6}	10^{-13}

[a] This work. [b] Data from ref 7, for R = *tert*-butyl, $k = 3.2 \times 10^{-4}\ s^{-1}$. [c] Data from ref 7. [d] Data from ref 6.

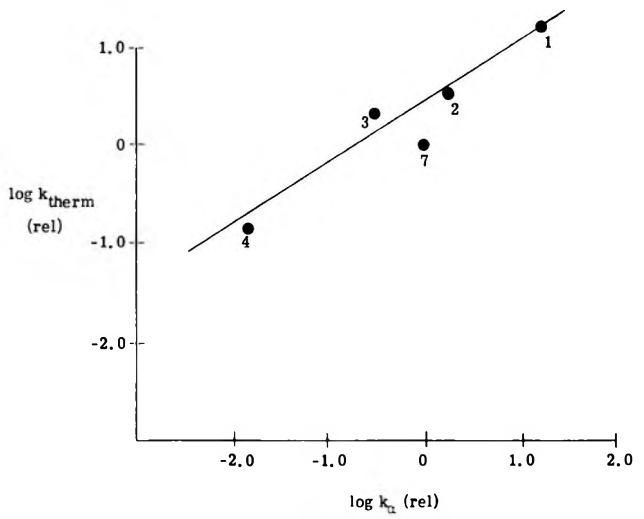


Figure 1. Linear free energy relationship for photochemical α-cleavage and perester thermolysis (Table III).

substrates and corresponding carbonium ions. Rüchardt[7,8] has found a good linear free energy relationship between the rate constants for bridgehead bromide solvolysis and perester thermolysis, the latter reaction being considerably less sensitive to ring strain (Table III). Rüchardt[8] attributes the variation in bridgehead perester reactivity to polar effects rather than ring strain. In support of this theory, a decrease of perester rate constants with increasing s character of the exocyclic bridgehead bond, as measured by the ^{13}C–H coupling constants of the corresponding polycyclic alkanes, is observed.

Both solvolysis of alkyl bromides[6] and thermolysis of azoalkanes[7,8] are subject to large rate retardation, even for 1-adamantyl vs. *tert*-butyl. These results are consistent with an almost planar transition state possessing considerable angle strain. In contrast, neither photochemical α-cleavage nor perester thermolysis[7] are subject to substantial retardation even for the bicyclo[2.2.2] substrates. Modest rate enhancements are observed for the homoadamantyl substrates, the effect being larger for the 3-homoadamantyl substrates.[17] The linear free energy relationship between ketone α-cleavage and perester thermolysis[7] is shown in Figure 1. We note that ketone α-cleavage is somewhat more sensitive to bridgehead alkane structure than is perester thermolysis, even though the rate constants for the photochemical reaction are 10^{10} faster. There is evidence that all of the peresters in Table III thermolyze via a one-step mechanism.[18] Therefore extrapolation of the data in Figure 1 to obtain values of k_α for ketones **5** and **6** appears justified. The estimated values of k_α for ketones **5** and **6** (10^4 and 10^2 s^{-1}, respectively) are substantially lower than typical values for alkyl phenyl ketone nonradiative decay in benzene solution ($\sim 3 \times 10^5$ s^{-1}).[12] Thus the insignificant α-cleavage of **5** and the complete lack of α-cleavage of **6** are not surprising. In view of the similar effects of structure on reactivity for ketone α-cleavage and perester thermolysis, Rüchardt's postulate of a polar transition state for homolysis may apply to photochemical α-cleavage. A polar transition state is consistent with our previous observations for deoxybenzoin derivatives.[4,5]

Photoreduction does not compete with α-cleavage of ketones **1**–**3** even in 2-propanol solvent. Scavenging of the bridgehead free radicals by 2-propanol provides another useful method of preparing the polycyclic hydrocarbons.[19] If the bridgehead phenyl ketones abstract hydrogen from 2-propanol with rate constants similar to that for pivalophenone (2.4×10^4 M^{-1} s^{-1}),[12] ~5% photoreduction products would be expected for ketone **3** and <1% for ketones **1** and **2**. The lifetimes of ketones **4** and **5** are sufficiently long to allow photoreduction to compete efficiently with α-cleavage. Photoreduction is the exclusive reaction for ketone **6** in 2-propanol, as is the case for acetophenone.[12]

Experimental Section

General procedures for purification of materials,[3] quantum yield measurements,[3] Stern–Volmer quenching,[3] and room temperature phosphorescence lifetime and quantum yield measurements[4] have been previously described. Product analysis of preparative photolysis mixtures employed a Hewlett-Packard 5700 thermal conductivity gas chromatograph with a 3 m × 2.5 mm stainless-steel column containing 4% Apiezon L on DMCA-AW Chromosorb G. Mass spectra were recorded using a EAI Quad 150 spectrometer.

3-Benzoylhomoadamantane (1). To a solution of 68.0 g (0.35 mol) of homoadamantane-3-carboxylic acid[20] in 1 l. of absolute tetrahydrofuran at −60 °C was added a solution of phenyllithium (1.1 l., 0.76 M) within 4 h. After additional stirring for 1 h at 20 °C the reaction mixture was poured onto ice and extracted with ether. The ethereal phase was washed with 5% aqueous NaOH and water and yielded 120 g of viscous residue. Purification by treatment with Girard T[21] reagent and subsequent distillation yielded 37.6 g of pure 3-benzoylhomoadamantane which was once crystallized from CH_3OH: mp 68 °C; ir (KBr) 1675 cm^{-1}; ^1H NMR (CCl_4) δ 1.86 (m, 17 H), 7.4 (m, 3 H), 7.64 (m, 2 H). Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.7; H, 8.47.

Oxime: mp 213–215 °C (from ethanol). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.1; H, 8.66; N, 5.28.

2,4-Dinitrophenylhydrazone: mp 222–223 °C (from ethanol). Anal. Calcd for $C_{24}H_{26}N_4O_4$: C, 66.34; H, 6.03; N, 12.9. Found: C, 66.45; H, 5.94; N, 12.8.

1-Benzoylhomoadamantane (2). To a solution of 68.0 g (0.35 mol) of homoadamantane-1-carboxylic acid[20] in 1000 ml of absolute tetrahydrofuran at −60 °C was added a solution of phenyllithium (900 ml of ethereal solution, 0.8 M). After stirring for 2.5 h at 20 °C the reaction mixture was poured onto ice and extracted with ether. Workup as previously described yielded 100 g of residue. Purification by treatment with Girard T[21] and subsequent distillation yielded after crystallization from CH_3OH (twice) 40.7 g of pure 1-benzoylhomoadamantane: mp 55–56 °C; ir (KBr) 1675 cm^{-1}; ^1H NMR (CCl_4) δ 1.83 (m, 17 H), 7.4 (m, 5 H). Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.85; H, 8.64.

Oxime: mp 195–196 °C (from ethanol). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.24; H, 8.61; N, 5.20. Found: C, 80.25; H, 8.91; N, 5.21.

2,4-Dinitrophenylhydrazone: mp 238–239 °C (from ethanol/benzene). Anal. Calcd for $C_{24}H_{26}N_4O_4$: C, 66.34; H, 6.03; N, 12.90. Found: C, 66.8; H, 6.00; N, 12.85.

1-(α-Hydroxybenzyl)homoadamantane was prepared by $NaBH_4$ reduction of 1-benzoylhomoadamantane in CH_3OH at 20 °C. The alcohol did not crystallize. It was distilled bulb to bulb: bp 170 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 7.2 (s, 5 H), 4.17 (s, 1 H), 1.0–2.2 (m, 18 H, including OH). Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.6; H, 9.15.

1-Benzoyladamantane (3) was synthesized from adamantane-1-carbonic acid chloride and diphenylcadmium by the method of Stetter.[22] Separation of biphenyl was achieved by treatment of the crude ketone mixture with Girard T:[21] mp 55–56 °C; ^1H NMR (CCl_4) δ 1.76 (s, 6 H), 2.0 (s, 9 H), 7.4 (m, 5 H).

1-Benzoylbicyclo[2.2.2]octane (4). A. A mixture of 111.0 g (0.72 mol) of bicyclo[2.2.2]octane-1-carboxylic acid[23] and 130.0 g (1.08 mol) of $SOCl_2$ was refluxed for 2 h. Fractional distillation yielded 116.1 g (94%) of bicyclo[2.2.2]octane-1-carboxylic acid chloride: bp 101–103 °C (13 mm); n^{20}D 1.5005. Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.54; Cl, 20.58. Found: C, 62.55; H, 7.67; Cl, 20.90.

B. According to Stetter[22] a solution of 115.0 g (0.7 mol) of bicyclo[2.2.2]octane-1-carboxylic acid chloride in 500 ml of benzene was added within 15 min to a 500-ml benzene solution of diphenylcadmium, prepared from a Grignard solution of 1 mol of Mg and 1 mol of phenyl bromide in absolute ether and 0.53 mol of $CdCl_2$. After refluxing the mixture for 2 h ice/2 NH_2SO_4 was added. The organic layer was separated, washed with 2 N NaOH, 1 N HCl, and water, and then dried over Na_2SO_4. Crystalline material (134 g) was isolated, which on purification by Girard T treatment,[21] crystallization, and zone refining yielded 102 g of pure 1-benzoylbicyclo[2.2.2]octane: mp 57–58 °C; ir (KBr) 1660 cm^{-1}; ^1H NMR (CCl_4) δ 1.71 (m, 13 H), 7.4 (m, 5 H). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.10; H, 8.38.

Oxime: mp 228–229 °C (from ethanol). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.30; H, 8.37; N, 6.07.

2,4-Dinitrophenylhydrazone: mp 248–249 °C (from ethanol/

benzene). Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.94; H, 5.62; N, 14.21. Found: C, 63.90; H, 5.70; N, 14.0.

1-(α-Hydroxybenzyl)bicyclo[2.2.2]octane was prepared by $NaBH_4$ reduction of 1-benzoylbicyclo[2.2.2]octane in CH_3OH at 20 °C: mp 99–101 °C (from *n*-hexane); ^1H NMR ($CDCl_3$) δ 9.56 (m, 13 H), 1.95 (s, OH), 4.22 (s, 1 H), 7.22 (m, 5 H). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.15; H, 9.33.

1-Benzoylbicyclo[3.2.1]octane (5). A. Bicyclo[3.2.1]octane-1-carboxylic acid[24] (147.6 g, 0.96 mol) and 160.0 g (1.3 mol) of $SOCl_2$ were refluxed for 2 h. Fractional distillation yielded 152.3 g (93%) of bicyclo[3.2.1]octane-1-carboxylic acid chloride, bp 75–80 °C (1.3 mm). Anal. Calcd for $C_9H_{13}ClO$: C, 62.60; H, 7.53; Cl, 20.59. Found: C, 62.75; H, 7.51; Cl, 20.2. A small amount of the acid chloride was treated with CH_3OH and the methyl ester formed analyzed by GC for the presence of 2-carbomethoxybicyclo[2.2.2]octane. The methyl ester formed consisted only of 1-carbomethoxybicyclo[3.2.1]octane.

B. To a 600-ml benzene solution of diphenylcadmium, prepared from 1.1 mol of Mg and 1.1 mol of phenyl bromide in ether and 0.56 mol of $CdCl_2$, was added within 15 min a solution of 131.4 g (0.76 mol) of bicyclo[3.2.1]octane-1-carboxylic acid chloride in 600 ml of benzene. After refluxing for 2 h the mixture was worked up as usual. Unreacted bicyclic acid (29.0 g) and 175.1 g of ketonic material were obtained. Further purification by treatment with Girard T[21] and distillation yielded 149.2 g of pure 1-benzoylbicyclo[3.2.1]octane: bp 129–133 °C (0.4 mm); $n^{20}D$ 1.5575; ir ($CHCl_3$) 1680 cm^{-1}; ^1H NMR (CCl_4) δ 1.7 (m, 10 H), 2.35 (m, 1 H), 7.4 (m, 3 H), 7.84 (m, 2 H). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.41. Found: C, 84.00; H, 8.48.

Oxime: mp 191–192 °C (from ethanol). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.70; H, 8.51; N, 6.03.

2,4-Dinitrophenylhydrazone: mp 217.5–219 °C (from ethanol). Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 63 94; H, 5.62; N, 14.21. Found: C, 64.00; H, 5.60; N, 14.40.

1-(α-Hydroxybenzyl)bicyclo[3.2.1]octane was prepared by $NaBH_4$ reduction of 1-benzoylbicyclo[3.2.1]octane in CH_3OH at 20 °C: mp 62–64 °C (from *n*-hexane); ^1H NMR ($CDCl_3$) δ 1.0–2.3 (m, 13 H), 2.1 (s, 1 H), 4.44 (s, 1 H), 7.25 (s, 5 H). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.7; H, 9.49.

1-Benzoylbicyclo[2.2.1]heptane (6). To a solution of 91.0 g (0.72 mol) of bicyclo[2.2.1]heptane-1-carboxylic acid[25] in 1.8 l. of absolute tetrahydrofuran was added within 1 h under nitrogen and stirring a solution of phenyllithium in ether (1.1 M, 1.25 l.) at −60 °C. The mixture was stirred for another 1 h at 25 °C and poured onto ice. Usual workup yielded 11.5 g of unreacted acid and 135.0 g of yellowish oil. Further purification of the impure ketone by treatment with Girard T[21] and distillation yielded 96.4 g of pure 1-benzoylbicyclo[2.2.1]-heptane: mp 32–34 °C (from *n*-hexane/ether); bp 105–107 °C (0.25 mm); ir (CCl_4) 1675 cm^{-1}; ^1H NMR (CCl_4) δ 1.68 (m, 13 H), 7.23 (m, 3 H), 7.67 (m, 2 H). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.90; H, 8.14.

2,4-Dinitrophenylhydrazone: mp 174–175 °C (from ethanol) (lit.[26] mp 198–199 °C). Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.25; H, 5.39; N, 14.6.

1-(α-Hydroxybenzyl)bicyclo[2.2.1]heptane was prepared by $NaBH_4$ reduction of 1-benzoylbicyclo[2.2.1]heptane in CH_3OH at 20 °C: mp 99–101 °C (from *n*-hexane) (sublimation): ^1H NMR ($CDCl_3$) δ 0.85–1.75 (m, 10 H), 2.10 (s, OH), 2.2 (m, 1 H), 4.8 (s, 1 H), 7.27 (m, 5 H). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.8; H, 8.87.

Photolysis of Ketones 1–5. Solutions (0.01 M) of **1–5** in benzene were irradiated (Philips HPK 125 W, GWCa filter, transparent for λ > 330 nm under nitrogen atmosphere). The disappearance of ketone was followed by GC. After most of ketone **1** had disappeared, the photolyses were stopped and the reaction mixtures analyzed using a combination of GC and mass spectrometer. Yields are reported as uncorrected GC peak areas.

3-Benzoylhomoadamantane (1) gave besides unreacted **1** (5.8%), benzaldehyde (8.2%), homoadamantane (54.9%), benzophenone (2.8%), and 3-phenylhomoadamantane (3.5%).

1-Benzoylhomoadamantane (2) gave besides unreacted **2** (8%), benzaldehyde (9.0%), homoadamantane (39.7%), benzophenone (4.2%), and 1-phenylhomoadamantane (34.2%).

1-Benzoyladamantane (3) gave besides unreacted **3** (50%), benzaldehyde (10.8%), adamantane (12.8%), benzophenone (1%), and 1-phenyladamantane (25%).

1-Benzoylbicyclo[2.2.2]octane (4) gave besides unreacted **4** (~90%), bicyclo[2.2.2]octane (~1%), benzaldehyde (~1%), benzophenone (<0.5%), and 1-phenylbicyclo[2.2.2]octane (7%).

1-Benzoylbicyclo[3.2.1]octane (5) gave besides unreacted **5** (59%), bicyclo[3.2.1]octane (traces), benzaldehyde (traces), benzophenone (traces), and acetophenone (~2%).

Benzaldehyde from photolysis of ketones **1–4** was captured as its 2,4-dinitrophenylhydrazone and identified. For ketone **5** this procedure was unsuccessful; the only 2,4-dinitrophenylhydrazone isolated was the derivative of acetophenone. The hydrocarbons from photolysis of ketones **1–4** were isolated and identified by comparison with authentic samples after being separated from the reaction mixture by chromatography on silica gel with *n*-hexane, which provided a mixture of polycyclic alkane and its phenyl derivative. The polycyclic hydrocarbon was separated from the phenyl derivative by simple sublimation. Only in the case of photolysis of 1-benzoyladamantane was the corresponding 1-phenyladamantane isolated and identified by mixture melting point with an authentic sample.[27]

Photoreduction of 1-Benzoylhomoadamantane (2). A solution of 2.0 g of 1-benzoylhomoadamantane in 200 ml of 2-propanol was irradiated (Philips HPK 125 W, Pyrex) under nitrogen for 20 H. Control by TLC revealed no evidence for the formation of pinacols or 1-(α-hydroxybenzyl)homoadamantane. Evaporation of the solvent yielded a crystalline residue which on chromatography (silica gel) with *n*-hexane yielded 0.65 g of homoadamantane, mp 248–251 °C. Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.59; H, 11.87.

Photoreduction of 3-Benzoylhomoadamantane (1). Ketone (2.0 g) was reduced in 2-propanol as described above. Chromatography yielded 0.74 g of homoadamantane, which proved to be identical by ir spectrum with the material isolated from 1-benzoylhomoadamantane irradiation.

Photoreduction of 1-Benzoyladamantane (3). A solution of 2.0 g of 1-benzoyladamantane in 200 ml of 2-propanol was irradiated as described above. Monitoring by TLC showed that there was no formation of 1-(α-hydroxybenzyl)adamantane.[28] Evaporation of the solvent left a crystalline residue which on chromatography (silica gel elution with *n*-hexane) yielded 0.8 g of adamantane, identified by GC comparison with an authentic sample. Further elution with more polar solvents yielded no other identifiable products.

Photoreduction of 1-Benzoylbicyclo[2.2.2]octane (4). A solution of 5.35 g of 1-benzoylbicyclo[2.2.2]octane in 250 ml of 2-propanol was irradiated as described above for 24 h. Evaporation of the solvent yielded 4.85 g of brownish crystals which on treatment with 2-propanol yielded 0.12 g of crystals of unknown structure, mp 230–235 °C (sublimation). The filtrate was evaporated and residue separated by chromatography on silica gel to yield 1.7 g of pinacols, mp 137–139 °C. Anal. Calcd for $C_{30}H_{38}O_2$: C, 83.67; H, 8.90. Found: C, 83.55; H, 8.77.

Further elution yielded 0.65 g of unreacted **4**. Qualitatively it was observed that the ketone even when irradiated in 2-propanol underwent α-cleavage. Bicyclo[2.2.2]octane was found by GC analysis.

Photoreduction of 1-Benzoylbicyclo[3.2.1]octane (5). A solution of 5.35 g of 1-benzoylbicyclo[3.2.1]octane in 250 ml of 2-propanol was irradiated as described above for 24 h. A precipitate (0.2 g, mp 177–178 °C, sealed capillary) was separated and the filtrate evaporated. The oily residue (4.55 g) was analyzed for pinacols and secondary alcohol by TLC. Chromatography on silica gel yielded 1.2 g of crystalline pinacols, mp 129–133 °C. Anal. Calcd for $C_{30}H_{38}O_2$: C, 83.67; H, 8.90. Found: C, 83.74; H, 8.63.

Further elution yielded 0.78 g of starting material, followed by 0.5 g of 1-(α-hydroxybenzyl)bicyclo[3.2.1]octane, identified by mixture melting point and TLC with an authentic sample. As for ketone **5**, the photoreduction gave a complex mixture, α-cleavage products being detected by GC.

Photoreduction of 1-Benzoylbicyclo[2.2.1]heptane (6). A solution of 2.0 g of ketone in 200 ml of 2-propanol was irradiated (Philips HPK 125 W, Pyrex) under nitrogen for 16 h. Evaporation of the solvent yielded a crystalline residue which was separated on silica gel. Elution with benzene/*n*-hexane yielded 1.5 g of pincaols, mp 225–240 °C. Further elution with benzene yielded 0.35 g of 1-(α-hydroxybenzyl)bicyclo[2.2.1]heptane, identified by elemental analysis and by comparison of mixture melting point and ir spectroscopic data with an authentic sample. An attempt was made to separate the diastereomeric pinacols. One isomer was isolated in pure form, mp 233–234 °C (sealed capillary). Anal. Calcd for $C_{28}H_{34}O_2$: C, 83.54; H, 8.51. Found: C, 83.5; H, 8.50.

When a solution of 2.0 g of ketone in 200 ml of 2-propanol containing 2 ml of piperylene was irradiated under the same conditions, no photoreduction was observed. Similar results were obtained when 1-benzoylbicyclo[3.2.1]octane or -bicyclo[2.2.2]octane were irradiated in 2-propanol containing 2% piperylene.

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Registry No.—**1**, 58541-21-2; 1 oxime, 58541-22-3; 1 2,4-DNPH, 58541-23-4; **2**, 58541-24-5; **2** oxime, 58541-25-6; **2** 2,4-DNPH, 58541-26-7; **3**, 31919-47-8; **4**, 58541-27-8; **4** oxime, 58541-28-9; **4** 2,4-DNPH, 58541-29-0; **5**, 58541-30-3; **5** oxime, 58541-31-4; **5** 2,4-DNPH, 58541-32-5; **6**, 1015-14-1; **6** 2,4-DNPH, 58541-33-6; **7**, 938-16-9; **8**, 98-86-2; homoadamantane-3-carboxylic acid, 21898-91-9; homoadamantane-1-carboxylic acid, 31061-65-1; 1-(α-hydroxybenzyl)homoadamantane, 58541-34-7; adamantane-1-carbonic acid chloride, 2094-72-6; bicyclo[2.2.2]octane-1-carboxylic acid, 699-55-8, bicyclo[2.2.2]octane-1-carboxylic acid chloride, 21891-38-3; 1-(α-hydroxybenzyl)bicyclo[2.2.2]octane, 5818-96-2; bicyclo[3.2.1]octane-1-carboxylic acid, 2534-83-0; bicyclo[3.2.1]octane-1-carboxylic acid chloride, 58541-35-8; 1-(α-hydroxybenzyl)bicyclo[3.2.1]octane, 58541-36-9; bicyclo[2.2.1]heptane-1-carboxylic acid, 18720-30-4; 1-(α-hydroxybenzyl)bicyclo[2.2.1]heptane, 5818-94-0; homoadamantane, 281-46-9.

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Bridged Polycyclic Compounds. 82. Multiple Mechanisms for Oxymercuration of Some Dibenzobicyclo[2.2.2]octatrienes[1]

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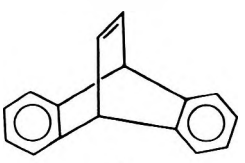
Addition of mercuric acetate to 1-methyldibenzobicyclo[2.2.2]octatriene, 1-methoxydibenzobicyclo[2.2.2]octatriene, and 1,4-dimethyldibenzobicyclo[2.2.2]octatriene has been carried out in a variety of solvent systems. With variation in substrate and in reaction conditions, cis addition, trans addition, and addition with rearrangement have been observed. The composition of the product mixtures have been rationalized in terms of these competing reaction paths for oxymercuration.

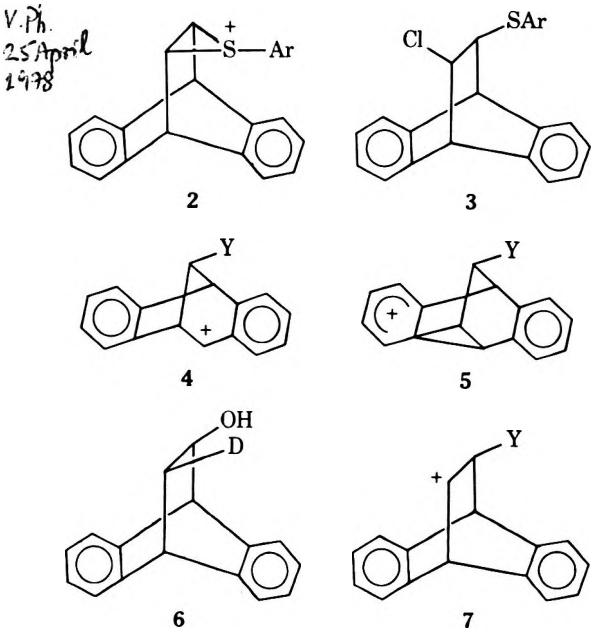
There has been much recent interest in oxymercuration reactions because of their usefulness in synthesis and their interesting mechanistic possibilities.[2] It has been suggested that oxymercuration proceeds via mercurinium ions, via concerted additions, and via β-mercuricarbocations, and a good deal of effort has been extended to prove or disprove the intervention of one or more of these intermediates or processes.

It seemed to us that a conservative viewpoint would assume that there are many mechanisms for oxymercuration reactions, just as for other electrophilic addition reactions. Our experience with dibenzobicyclo[2.2.2]octatriene (1) and related compounds suggested that this would be a useful system to investigate, as small modifications of structure or of reaction conditions often lead to mechanistic changes. The results of a portion of our studies are reported in this paper.



1

Although anti addition to 1 is quite rare, it does occur when onium ion intermediates intervene and are attacked directly by nucleophiles. Thus addition of arenesulfenyl chlorides proceeds via the sulfonium ions **2**, to give trans addition

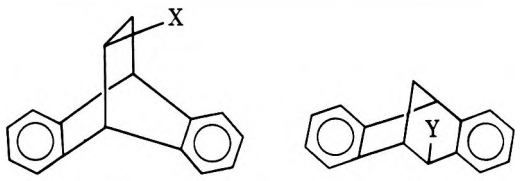


2 3 4 5 6 7

products **3**.[3] The fact that anti addition is generally not observed in these systems[4,5] suggests either that onium ions analogous to **2**, but with other heteroatoms, are often not involved[1] or that the reactivity toward displacements at the gunwale positions of the boat-form cyclohexane rings is small. Onium ions can then open with rearrangement to [3.2.1] cations, such as **4**, or to bridged cations **5**, which then give rearranged products. This has been noted even when sulfonium-ion intermediates are possible.[6]

Concerted bimolecular addition processes lead directly to syn products, exemplified by addition of deuteriodiborane to **1**, which gives *cis*-3-deuteriodibenzobicyclo[2.2.2]octadien-2-ol **6** upon oxidation of the intermediary organoborane.[7]

Open secondary cations of type **7** are of relatively high energy and are rarely observed,[7] while intermediates of type **4** or **5** are utilized in carbocationic pathways.[1] The solvolyses of **8** species invariably yield [3.2.1] products **9** through kinetic



control.[3,8,9] These are sometimes admixed with endo products **10**, and are rapidly converted to equilibrium mixtures with **10**. Such mixtures can generally be stereospecifically reisomerized to the [2.2.2] system. Additions follow similar paths, if carbocations are involved, giving [3.2.1] products. Thus additions to **1** of iodine and silver acetate, bromine in acetic acid, chlorine in carbon tetrachloride, and *tert*-butyl hypochlorite in acetic acid lead to the products **11** with the electrophile X at the syn-8 position, and the nucleophile Y at the benzylic position.

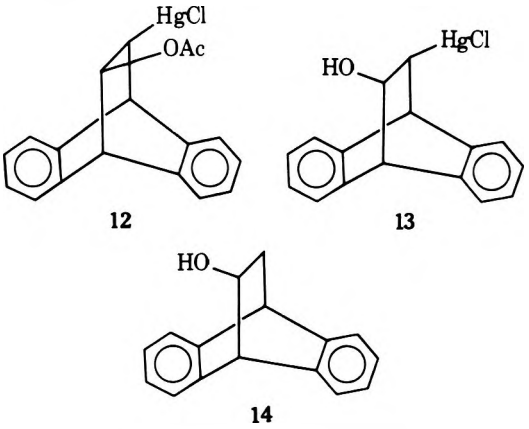
From such observations, it is clear that product studies may be used to determine addition reaction mechanisms. A reaction giving a cis-[2.2.2] product may be assumed to involve a cyclic mechanism, one giving a trans-[2.2.2] product must involve nucleophilic attack on an onium ion, and a [3.2.1] product establishes the intervention of a carbocation.

Much work has been reported supporting various mechanisms of oxymercuration. Lucas, Hepner, and Winstein[10] demonstrated reversible complex formation between mercuric ion and olefins. They proposed that the complexes were mercurinium ions and that they were intermediates in oxymercuration reactions, predicting correctly that the stereospecificity noted[11] in the methoxymercuration of cyclohexene would be that of anti addition. Many examples of anti addition have been since reported;[2] these seem clearly understandable as products of direct displacement (with inversion) on mercurinium ions.[2c] Bach and Richter[12] presented evidence supporting such a process in which ion formation is fast and reversible, and the rate-determining step is ligand or solvent attack.

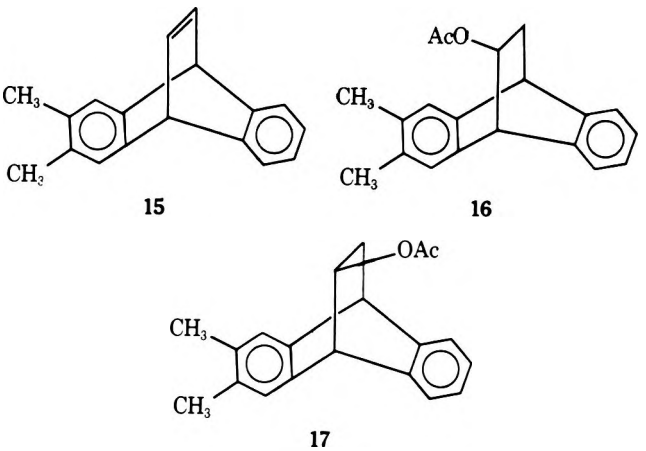
While Kitching, Smith, and Wells[13] were unable to find ^{1}H NMR evidence for stable mercurinium ions, Olah and Clifford[14] did observe the ^{1}H NMR spectrum of the mercurinium ions formed in superacid solutions at −30 °C from 2-methoxyethylmercuric chloride and at −70 °C from *exo-cis*-3-hydroxy-2-norbornylmercuric chloride. Whitham[15] failed to find evidence for a mercurinium ion by a trapping experiment involving acid-catalyzed methanol–H_2O exchange. That experiment is consistent with a rapid equilibration between mercurinium ion and liganded mercuric ion and olefin, or with the nonexistence of mercurinium ions, as are the kinetic data of Halpern[16] and the experiment of Sokolov, Troitskaya, and Reutov.[17]

Traylor[18] noted that norbornene and substituted norbornenes add mercuric acetate or the elements of methoxymercuric acetate in a cis-exo fashion, even with large syn-7 substituents, and proposed a concerted cyclic mechanism. Brown and Kawakami[19] noted similar results, which they assume ruled out mercurinium ions in the syn-7-methyl case. As 2-methylnorbornene gave Markownikoff addition, they proposed that a mercuricarbenium ion must be involved rather than a cyclic process, although experience in Brown's laboratory with hydroboration reactions[20] seems to have been ignored in this interpretation.

Previous work with **1** indicates the occurrence of at least two mechanisms for oxymercuration. Sokolov[21] reported that, in acetic acid, oxymercuration of **1** gave only the cis product **12**,

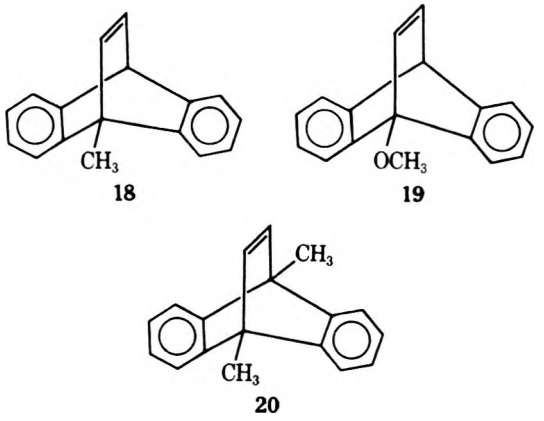


while in aqueous acetone both cis and trans addition occurred, giving the acetate **12** and the alcohol **13** in a 70:30 ratio. We have now confirmed these results and have shown that no rearrangement occurred in the reaction in aqueous acetone by reducing the mixture of mercurials with sodium borohydride to the alcohol **14**, without any **9**-OH or **10**-OH being produced. In acetic acid a cyclic process apparently obtains, while in aqueous acetone there is competition between a cyclic and a mercurinium ion process. The reaction of **15** with mercuric acetate in acetic acid, followed by hydrodemercuration with sodium borohydride, gave acetates **16** and **17** in equal amounts.[1] This result was similarly interpreted as evidence for cyclic processes involving molecular addition of mercuric acetate.



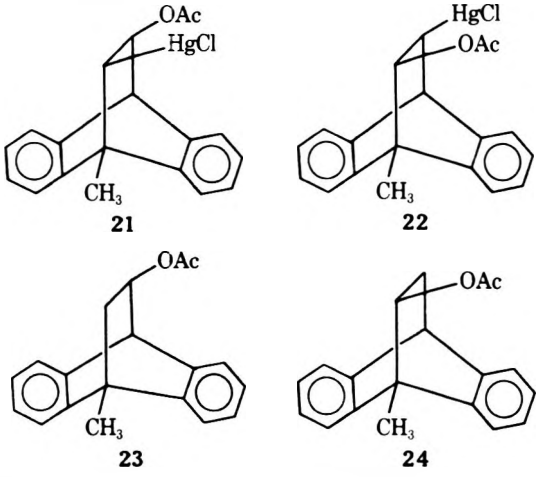
We have now examined the addition of mercuric acetate in

various solvents to 1-methyldibenzobicyclo[2.2.2]octatriene (**18**), 1-methoxydibenzobicyclo[2.2.2.]octatriene (**19**), and 1,4-dimethyldibenzobicyclo[2.2.2]octatriene (**20**).



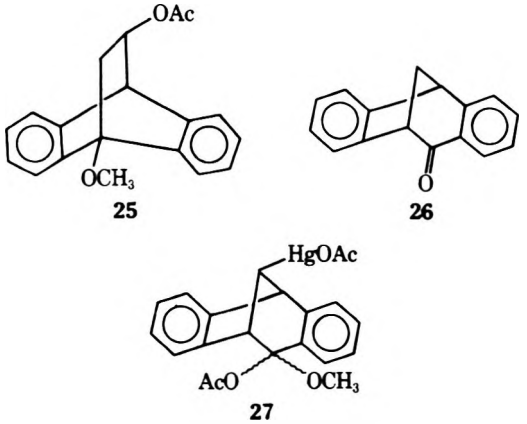
18 **19** **20**

When addition of mercuric acetate to **18** was carried out in acetic acid and the products isolated as the chloromercurials, cis [2.2.2] addition products **21** and **22** were observed (^{1}H NMR) in a 3:2 ratio, respectively. This ratio was confirmed by hydrodemercuration of the product which gave a mixture of acetates **23** and **24** in which **23** predominated. Here, then, syn addition occurred, giving both of the anticipated products. We note that the electrophilic atom adds principally closer to the 9-methyl substituent, but offer no rationalization for this.



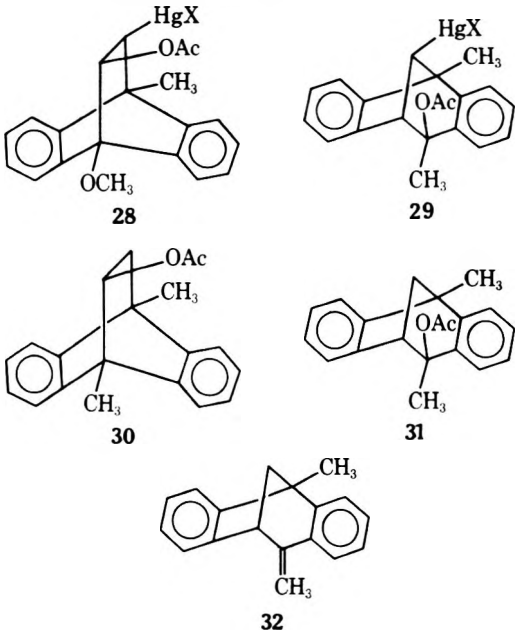
21 **22** **23** **24**

19 was treated with mercuric acetate in acetic acid, and the mixture subjected to hydrodemercuration. The principal (ca. 66%) product was **25**, which again resulted from an addition (presumably syn) process in which the electrophilic atom attacked the atom closer to the 9 substituent. The minor product was **26**, which may be presumed to be formed via **27** in the work-up and reduction. With **19** we see the very interesting result that the consequence of attachment of electrophile to one end of a double bond is syn attachment of nucleophile, while the consequence of attachment of electrophile at the other end is a carbenium-ion rearrangement.



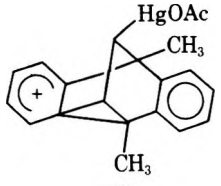
25 **26** **27**

With **20**, mercuric acetate in acetic acid gave two products, **28**-OAc and **29**-OAc, when the reaction time was short (1 h).



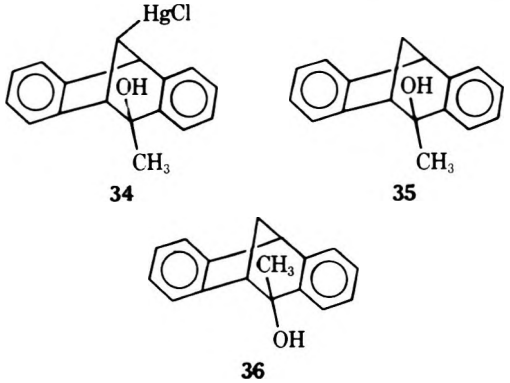
28 **29** **30** **31** **32**

With longer times (1 day), the product was largely **28**-OAc. The existence of both **28** and **29** was confirmed by reduction to **30** and **31**, along with the olefin **32**. The transformation of **20** to **29** as a substantial product of a short reaction time process indicates that in this system addition leads to a carbenium ion, which gives **29**-OAc, about as fast as **20** reacts by a syn process to give **28**-OAc. **29**-OAc is unstable to reaction conditions and (see below) reverts to starting olefin and mercuric acetate which again distributes itself between **28** and **29**, ultimately giving principally **28**. It is also possible that some **28** arises via ion **33**, in a process analogous to many such rearrangements.[22]



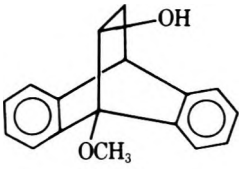
33

In view of the results in acetic acid, we decided to investigate additions in other solvents and in mixed solvents. With mercuric acetate in 50% aqueous acetone, **18** gave alcohol **34** as the predominant product. Hydrodemercuration of **34** gave the



34 **35** **36**

tertiary alcohol **35**. That the hydroxyl group was exo was concluded from the fact that addition of methylmagnesium iodide to **26** gave an epimeric product **36**. Hydrodemercuration of the product mixture from the addition gave a mixture of **35** (55%) and the [2.2.2] alcohols **37** and **38** (45%, ratio about 1:1).



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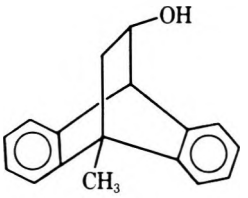

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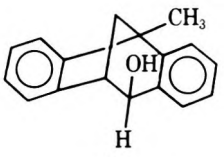

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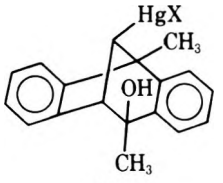
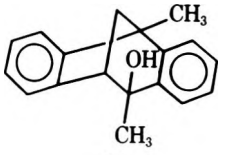


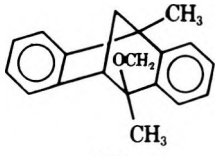
40

No alcohol **39** was present. The data do not indicate whether syn or anti addition occurred to give the progenitors of **37** and **38**, so that the processes competing with the carbenium ion rearrangement cannot be defined in this particular case, but clearly several mechanisms are operating.

Oxymercuration of **19** with mercuric acetate in 50% aqueous acetone, followed by hydrodemercuration gave **25** and **26** in about a 1:1 ratio. With **20**, only the rearranged alcohol **40**-Cl was formed, whose structure was confirmed by hydrodemercuration to **41**.



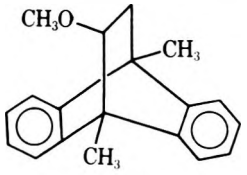
41



42

Addition of mercuric acetate to **18** and **20** was also carried out in 50% aqueous tetrahydrofuran. With **18**, the products identified after hydrodemercuration included alcohols **35**, **37**, and **38** along with acetates **23** and **24**. With **20** the sole product after hydrodemercuration was the [3.2.1] alcohol **41**, the result of a carbocation process.

Oxymercuration of **20** was carried out in a variety of other solvents. In 80% aqueous acetic acid, the only product after hydrodemercuration was the [3.2.1] alcohol **41**. In acetic acid–methanol (80:20), the only product after hydrodemercuration was the [3.2.1] ether **42**. When the reaction was carried out in acetic acid–methanol (95:5), the products isolated after reduction were the [3.2.1] ether **42**, the [2.2.2] acetate **30**, and olefin **32**. When the reaction was carried out in methanol, the products isolated after reduction were the [3.2.1] ether **42** and the [2.2.2] ether **43**. Isolation of **43** from the reduction does



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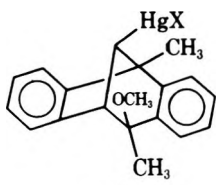
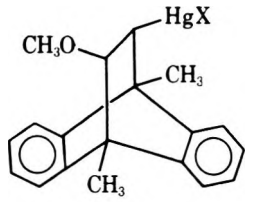
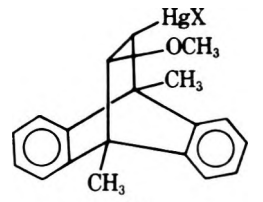


44

not tell whether the competition under these conditions is between the carbocation process which gives **44** and an anti process giving **45** or between the former and a syn process giving **46**. As noted above, anti processes are rare in these dibenzobicyclic systems, although Sokolov[21] did find such a process in the treatment of **1** with mercuric acetate in aqueous



45



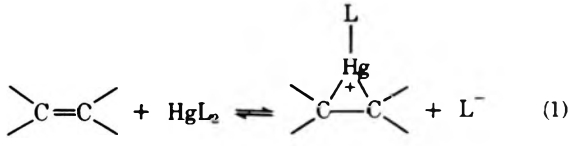
46

acetone mentioned above. That the anti process competes here as well was established by ^{1}H NMR analysis of the mixture of chloromercurial intermediates which clearly contained **44** and **45** and no detectable **46**. Hence the product is the result of an anti ring opening of a mercurinium ion intermediate and not that of a syn addition or of a rearrangement to **44** followed by the normal [3.2.1] → [2.2.2] rearrangement.[22]

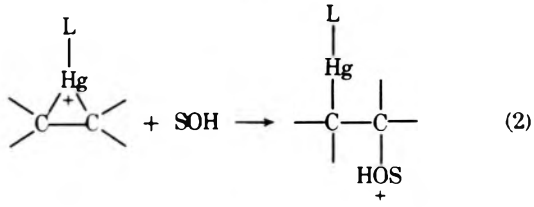
In order to verify the instability of **29**-OAc to oxymercuration conditions, addition of mercuric acetate to **20** in acetic acid was carried out and the **28**:**29** ratio was determined at various times. As **20** disappeared, **28** and **29** built up in amount at approximately the same rate (the **28**:**29** ratio being about 60:40) for about the first hour. After that, the **28**:**29** ratio increased until about 20 h and then remained relatively constant (**28**:**29** ratio being about 85:15). Since it was demonstrated that **28**-OAc was stable to reaction conditions, the **29**-OAc that was formed reverted to **20**, which then reacted again with mercuric acetate to form **28**-OA and **29**-OAc. For this reason, **28**-OAc was the predominant product observed in earlier experiments, which were carried out for long periods of time.

Conclusions

Analysis of the data presented compels a path in which the first step is a fast, reversible formation of a mercurinium ion (eq 1);[23] if capture of this species by solvent (eq 2) is relatively

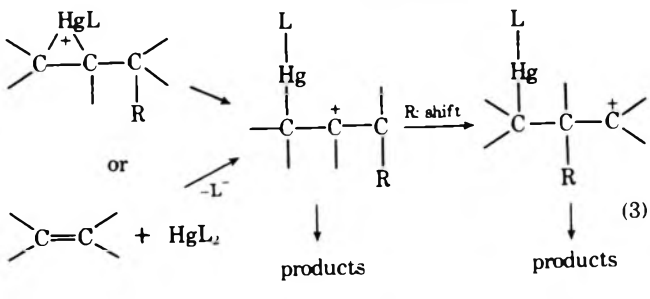


(1)



(2)

easy, the product isolated is the result of anti addition. If this step is very slow, then one or both of two additional reactions (eq 3 and 4) can occur. The pathways outlined in eq 3 may be



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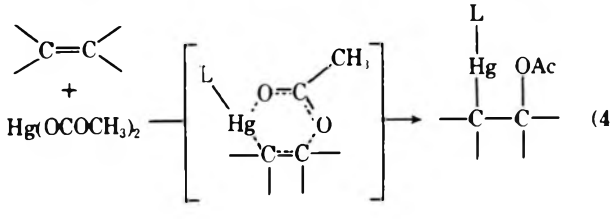

(4)

anticipated to occur in polar solvents, in particular when the solvent is relatively nonnucleophilic, and when a relatively stable carbocation is formed. It will be revealed when the product is that of a skeletal rearrangement and is stable under reaction conditions. It may also be occurring in cases where stereospecificity is not seen, although this may also be the result of a competition between the eq 2 and 4 pathways. The extra stability given to cation intermediates by the methyl or methoxy groups in **18, 19,** and **20** thus favors carbenium ion intermediates and leads to rearranged products, while none are observed with **1** or with the "unsubstituted" ends of the double bonds in **18** and **19.** Finally, a syn-concerted[18] addition process (eq 4) intervenes when neither the process of eq 2 nor that of eq 3 occurs readily. Just as in all concerted electrophilic additions, it seems likely that in the transition state of eq 4, carbon–electrophile bonding is advanced over carbon–nucleophile bonding[24] but obviously no carbocationic intermediate is involved.[26] Thus the differences between the processes represented in eq 1, 3, and 4 are subtle in nature, particularly as the mercuric ion begins to approach the double bond, but it is clear that these differences have profound effects, leading finally to different products.

Our system is one of the few in which rearrangement of the carbon skeleton has been noted to occur during oxymercuration. Although other cases are reported in the literature, all are in strained systems.[27-31]

Experimental Section

^{1}H NMR spectra were taken on a Varian A-60A spectrometer in $CDCl_3$ solution, unless otherwise indicated, with tetramethylsilane as an internal standard.[32] Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

1-Methyl-*trans*-7,8-dichlorodibenzobicyclo[2.2.2]octadiene (47). A mixture of 10 g (52 mmol) of 9-methylanthracene, 30 ml (0.39 mol) of *trans*-1,2-dichloroethene, and about 1 g of 4-*tert*-butylpyrocatechol was heated for 2 days at 180 °C in a sealed thick-wall Pyrex tube. The contents of the tube were chromatographed on 425 g of activated alumina, followed by elution with Skellysolve B. The product was recrystallized from ethanol to give two crops of large, white needles in 73% yield: mp 104–105 °C; ^{1}H NMR δ 7.10–7.50 (m, 8, aromatic H), 4.19–4.42 (m, 2, H-4 and H-8), 3.93 (d, 1, J = 2.8 Hz, H-7) and 2.00 ppm (s, 3, CH_3).

Anal.[34] Calcd for $C_{17}H_{14}Cl_2$: C, 70.60; H, 4.88. Found: C, 70.68; H, 4.97.

1-Methyl-*cis*-7,8-dichlorodibenzobicyclo[2.2.2]octadiene (48). A similar reaction with *cis*-1,2-dichloroethene gave **48** in 78% yield: mp 187–188 °C; ^{1}H NMR δ 7.08–7.53 (m, 8, aromatic H), 4.40–4.61 (m, 2, H-4 and H-8), 4.12 (m, 1, H-7), and 2.03 ppm (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{14}Cl_2$: C, 70.60; H, 4.88. Found: C, 70.56; H, 4.86.

1-Methyldibenzobicyclo[2.2.2]octatriene (18) was prepared by reduction of either **47** or **48** with zinc–copper couple in the usual fashion[33] for such reductions to give a 79% yield of **18**: mp 98–100 °C; ^{1}H NMR δ 6.8–7.4 (m, 9, aromatic H and H-8), 6.56 (d of d, 1, J = 7, 1.5 Hz, H-7), 5.04 (d of d, 1, J = 6 Hz, H-4), and 2.12 ppm (s, 3, CH_3).

Anal.[34] Calcd for $C_{17}H_{14}$: C, 93.94; H, 6.46. Found: C, 93.50; H, 6.41.

***trans*-7,8-Dichloro-1-methoxydibenzobicyclo[2.2.2]octadiene (50).** A mixture of 26.9 g (0.13 mol) of 9-methoxyanthracene (**49**), 1.0 g of hydroquinone, and 100 ml of *trans*-1,2-dichloroethane was heated in a sealed tube at 203° for 1 day. Workup as above for **47** gave 29 g (73%) of **50**: mp 134–135 °C; ^{1}H NMR δ 7.1–7.8 (m, 8, aromatic H), 4.2–4.4 (m, 3, H-4, H-7, and H-8), and 3.87 ppm (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{14}Cl_2O$: C, 66.89; H, 4.57; Cl, 23.28. Found: C, 67.01; H, 4.60; Cl, 23.38.

***cis*-7,8-Dichloro-1-methoxydibenzobicyclo[2.2.2]octadiene (51).** A similar reaction with *cis*-1,2-dichloroethene gave **51**: mp 169–170 °C; ^{1}H NMR δ 7.0–7.8 (m, 8, aromatic H), 4.40 (broad s, 1, H-4), 4.57 (broad s, 1, H-7), 4.60 (broad s, 1, H-8), and 3.92 ppm (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{14}Cl_2O$: C, 66.89; H, 4.57. Found: C, 66.73; H, 4.51.

1-Methoxydibenzobicyclo[2.2.2]octatriene (19). Reduction of **50** (or **51**) with zinc–copper couple[33] gave 80–85% of **19**: mp 174–175 °C; ^{1}H NMR δ 6.9–7.6 (m, 10, olefinic and aromatic H), 5.05 (d of d, 1, J = 5, 2 Hz, H-4), and 3.98 ppm (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{14}O$: C, 87.18; H, 5.98. Found: C, 87.28; H, 5.83.

***trans*-7,8-Dichloro-1,4-dimethyldibenzobicyclo[2.2.2]octadiene (53).** A mixture of 32.0 g (0.155 mol) of 9,10-dimethylanthracene (**52**),[35] 170 ml (213 g, 2 mol) of *trans*-1,2-dichlorethene, and 0.5 g of hydroquinone was heated at about 155 °C in a sealed glass tube for 2 days. Workup as usual gave 43.8 g (93%) of **53**: mp 135–137 °C; ^{1}H NMR δ 7.0–7.5 (m, 8, aromatic H), 3.80 (s, 2, H-7 and H-8), and 2.20 ppm (s, 6, CH_3).

Anal. Calcd for $C_{18}H_{16}Cl_2$: C, 71.31; H, 5.28; Cl, 23.41. Found: C, 71.22; H, 5.35, Cl, 23.66.

***cis*-7,8-Dichloro-1,4-dimethyldibenzobicyclo[2.2.2]octadiene (54)** was prepared in a similar fashion from *cis*-1,2-dichloroethane: mp 176–177 °C; ^{1}H NMR δ 7.0–7.5 (m, 8, aromatic H), 4.13 (s, 2, H-7 and H-8), and 2.0 ppm (s, 6, CH_3).

Anal. Calcd for $C_{18}H_{16}Cl_2$: C, 71.31; H, 5.28; Cl, 23.41. Found: C, 71.49; H, 5.36; Cl, 23.46.

1,4-Dimethyldibenzobicyclo[2.2.2]octatriene (20) was prepared by reduction of **53** with zinc–copper couple:[33] mp 117–119 °C; ^{1}H NMR δ 6.9–7.4 (m, 8, aromatic H), 6.62 (s, 2, olefinic H), and 2.12 ppm (s, 6, CH_3).

Anal. Calcd for $C_{18}H_{16}$: C, 93.10; H, 6.90. Found: C, 93.21; H, 6.97.

Addition of Mercuric Acetate to 1-Methyldibenzobicyclo[2.2.2]octatriene (18) in Acetic Acid Solvent. A solution of 327 mg (1.5 mmol) of **18** and 463 mg (1.45 mmol) of mercuric acetate in 15 ml of glacial acetic acid was stirred at room temperature for 3 h. Approximately 360 mg of NaCl was added, and the mixture was stirred for an additional 1 h. Water (35 ml) was added, producing a heavy precipitate, which was filtered 1 h later. The precipitate was washed with water and dried in vacuo to give 677 mg (91%). The ^{1}H NMR spectrum of this mixture showed some **18** plus the two cis adducts **21** and **22.** Planimeter integration of enlarged peaks determined the ratio of **21**:**22** to be 73 ± 4:27 ± 4. Repeated recrystallization from acetone–water gave 4-methyl-*cis*-8-chloromercuri-7-dibenzobicyclo[2.2.2]octadienyl acetate (**21**): mp 189.5–191.5 °C; ^{1}H NMR δ 7.0–7.5 (m, 8, aromatic H), 5.38 (d of d, 0.8 H, J = 8.5, 3 Hz, H-7), 4.69 (d, 0.8 H, J = 3 Hz, H-1), 3.15 (d, 0.8 H, J = 8.5 Hz, H-8), 2.06 (s, 3, $OCOCH_3$), and 1.96 ppm (s, 3, CH_3).

Anal. Calcd for $C_{19}H_{17}CLHgO_2$: C, 44.45; H, 3.34. Found: C, 44.43 H, 3.32.

Sodium Borohydride Reduction of the Acetoxymercuration Adducts of 18. To a mixture of 257 mg (0.5 mmol) of a product mixture similar to that described in the previous paragraph and of 12 mg (0.3 mmol) of sodium borohydride was added 2.0 ml of THF and 2.0 ml of 2 M NaOH. A rapid reaction occurred; the mixture was stirred for 20 min. Some chloroform and water were added, and the product was decanted from 89 mg (89%) of metallic mercury into 20 ml of water. The product was extracted with three 25-ml portions of chloroform. The chloroform extracts were washed with 25 ml of water and 25 ml of saturated aqueous NaCl and dried ($MgSO_4$). Evaporation of the chloroform gave 150 mg of an oil. The product was separated on a preparative TLC plate (silica gel G, 20 × 20 × 0.25 cm, developed with 10% ether in benzene), and the entire band of acetate products was collected (120 mg, 86%). ^{1}H NMR integration showed it to contain **23** and **24** in a ratio of 71:29, in good agreement with the ratios for **21** and **22.**

Oxymercuration of 20 in Acetic Acid for 1 h. Hydrodemercuration of 28-Cl and 29-Cl with Sodium Borohydride. A solution of 0.70 g (3 mmol) of **20** and 1.45 g (4.5 mmol) of mercuric acetate in 15 ml of glacial acetic acid was stirred for 55 min before 1.0 g (17 mmol) of NaCl was added. The solution was stirred for 5 min before 100 ml of water was added. The precipitate was collected, washed with water, and dried in vacuo over P_2O_5 for 1 day, to give 1.50 g (95%). The ^{1}H NMR spectrum of this product, in Me_2SO-d_6, showed the ratio of **28**:**29** to be 55:45 [from multiple integration of the absorptions of δ 5.34 (d, J = 9 Hz, H-7 of **28**) and 4.48 ppm (d, J = 5 Hz, H-1 of **29**)]. Approximately 15% of unreacted **20** remained. The product mixture (1.45 g, 2.85 mmol) was reduced with 0.20 g (5.3 mmol) of sodium borohydride in 15 ml of tetrahydrofuran and 15 ml of 2 M NaOH for 20 min. After the usual workup procedure, 0.85 g (about 100%) of an oil was obtained and the ratio of **30**:**31** was found to be 61:39 [multiple integrations of the absorptions at δ 4.88 (d of d, J = 9, 3 Hz, H-7 of **30**) with that at 4.37 ppm (d, J = 5 Hz, H-1 of **31**)]. Approximately 12% of the mixture was unreacted **20.**

Oxymercuration of 20 in Acetic Acid for Long Period of Time. Preparation of 28-Cl. A solution of 2.1 g (9 mmol) of **20** and 4.35 g (14.5 mmol) of mercuric acetate in 30 ml of glacial acetic acid was stirred for 19 h before 2.0 g (33 mmol) of NaCl was added. Workup as above, followed by recrystallization from aqueous acetone, gave 3.52 g (74%) of 1,4-dimethyl-*cis*-8-chloromercuri-7-dibenzobicy-

clo[2.2.2]octadienyl acetate (28): mp 204–205 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 7.18–7.58 (m, 8, aromatic H), 5.34 (d, 0.65 H, J = 9 Hz, H-7), 3.24 (d, 0.65 H, J = 9 Hz, H-8), 2.13 [s, 3, C(1) CH_3], 2.02 (s, 3, acetate CH_3), and 1.93 ppm [s, 3, C(4) CH_3].

1,4-Dimethyl-7-dibenzobicyclo[2.2.2]octadienyl Acetate (30). To 0.53 g (1 mmol) of 28-Cl in 10 ml of tetrahydrofuran and 10 ml of 2 M NaOH, 0.04 g (1 mmol) of sodium borohydride was added and the reaction mixture was stirred for 20 min. Usual workup gave 250 mg of an oil, whose ^{1}H NMR spectrum indicated that it was largely **30**, with small amounts of **32** and **20** also present. Crystallization and recrystallization from aqueous ethanol gave **30**: mp 96–97 °C; ^{1}H NMR δ 7.15–7.50 (m, 8, aromatic H), 4.92 (d of d, 1, J = 9, 3 Hz, H-7), 2.33 (d of d, 1, J = 14, 9 Hz, H-8 anti), 1.85–2.0 (m, 9, bridgehead and acetoxy CH_3), and 1.37 ppm (d of d, 1, J = 14, 3 Hz, H-8 syn).

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.19; H, 6.85. Found: C, 83.25; H, 6.65.

Oxymercuration–Hydrodemercuration of 1-Methoxydibenzobicyclo[2.2.2]octatriene (19) in Acetic Acid. A solution of 10.0 g (43 mmol) of **19** and 27.3 g (86 mmol) of mercuric acetate in 200 ml of glacial acetic acid was stirred for 2 days before 10.0 g of NaCl and 100 ml of water were added. Workup as above was followed by reduction with sodium borohydride in the normal fashion to give 14.3 g of an oil whose ^{1}H NMR spectrum showed **25** and **26** in a ratio of 2:1.

Oxymercuration of 18 in Acetone–Water. A 550-mg (2.30 mmol) sample of **18** was dissolved in 10 ml of acetone and, with stirring, 10.0 ml of distilled water and 0.5 ml of acetic acid were added. To this mixture was added 829 mg (2.6 mmol) of mercuric acetate. After 23 h, 600 mg of sodium chloride was added. The mixture was stirred for 15 min, and the turbid solution poured into 100 ml of water and extracted with three 75-ml portions of chloroform. Appropriate workup followed by recrystallization from chloroform–carbon tetrachloride gave *syn*-8-chloromercuri-*endo*-2-methyl-*exo*-2-dibenzobicyclo[3.2.1]octadienol (**34**): mp 220.2–221.8 °C dec; ^{1}H NMR δ 6.9–7.5 (m, 8, aromatic H), 4.10 (d, 0.8 H, J = 4 Hz, H-1), 3.48 (d, 0.8 H, J = 4.5 Hz, H-5), 3.22 (t, 0.8 H, J = 4.2 Hz, H-8 anti), 2.52 (s, 1, OH), and 1.55 ppm (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{15}ClHgO$: C, 43.32; H, 3.21. Found: C, 43.10; H, 3.14.

Hydrodemercuration of 34 with Sodium Borohydride. Treatment of **34** with sodium borohydride by the general treatment described above gave *endo*-2-methyl-*exo*-2-dibenzobicyclo[3.2.1]octadienol (**35**): mp 122–122.5 °C; ^{1}H NMR δ 6.9–7.5 (m, 8, aromatic H), 3.90 (m, 1, $W_{1/2}$ = 7 Hz, H-1), 3.29 (m, 1, $W_{1/2}$ = 7 Hz, H-5), 2.53 (m, 2, H-8), 2.15 (s, 1, OH), and 1.50 ppm (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.85. Found: C, 86.19; H, 7.09.

Hydrodemercuration of Products from Oxymercuration of 18 in Acetone–Water with Sodium Borohydride. After a mixture of 291 mg (1.0 mmol) of **18** and 319 mg (1.0 mmol) of mercuric acetate in 4 ml of acetone and 4 ml of water was stirred for 24 h, 2.0 ml of acetone and 2.0 ml of 6 M NaOH (aqueous) were added, followed by 38 mg (1.0 mmol) of sodium borohydride. The usual treatment and workup gave an oil (272 mg) from which 44 mg of **35** crystallized and was removed. Multiple integrations of the ^{1}H NMR spectrum (CCl_4) over the regions δ 3.3–4.2 (2 protons for both **37** and **38** and 1 proton for **35**) and 2.9–3.2 ppm (1 proton for **35**) allowed calculation of the ratio of **37** + **38**:**35**. The mixture consisted of 16% **18**, 46% **35**, and 38% **37** + **38**. The ratio of **37**:**38** could not be determined exactly, but was estimated at about 50:50. Addition of these data indicates that the original oxymercuration mixture showed an 85% reaction of **18** to give a 60:40 mixture of **34**:unrearranged hydroxy mercurials. Approximately 80% of the mercury added to the 8 carbon of **18**.

***exo*-2-Methyl-*endo*-2-dibenzobicyclo[3.2.1]octadienol (36).** A solution of 3.69 g (18 mmol) of dibenzobicyclo[3.2.1]octadien-4-one (**26**) in 70 ml of anhydrous ether was added to excess methylmagnesium iodide in ether and allowed to stand overnight at room temperature. Normal workup of Grignard reactions led to **36**, which after recrystallization from aqueous ethanol melted at 64–67°: ^{1}H NMR δ 6.9–7.5 (m, 8, aromatic H), 3.84 (d, J = 4.1 Hz, H-1), 3.35 (d, 1, J = 4.8 Hz, H-5), 2.63 (d of d of d, 1, J = 12.2, 4.8 Hz, 4.1 Hz, H-8 anti), 2.74 (d of t, 1, J = 11.2, 1 Hz, H-8 syn), and 1.74 ppm (s, 4, CH_3 and OH).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.85. Found: 86.62; H, 6.91.

Oxymercuration of 20 in Acetone–Water. Synthesis of *endo*-2,5-Dimethyl-*syn*-8-chloromercuri-*exo*-2-dibenzobicyclo[3.2.1]octadienol (40-Cl). A solution of 2.1 g (9 mmol) of **20** and 4.35 g (14.5 mmol) of mercuric acetate in 30 ml of acetone, 20 ml of water, and 0.5 ml of glacial acetic acid was stirred for 18 h. NaCl (2.0 g, 34 mmol) was added and stirred for 1 h. Workup gave, after recrystallization from chloroform–carbon tetrachloride, 3.60 g (82%) of **40**: mp 214–215 °C dec; ^{1}H NMR δ 6.7–7.7 (m, 8, aromatic H), 6.2 (s, 1, OH), 3.47 (d, 1, J = 5 Hz, H-1), 3.05 (d, 1, J = 5 Hz, H-8 anti), 1.83 [s, 3, C(2) CH_3], and 1.5 ppm (s, 3, bridgehead CH_3).

Anal. Calcd for $C_{18}H_{17}ClHgO$: C, 44.54; H, 3.50. Found: C, 44.35; H, 3.52.

***endo*-2,5-Dimethyl-*exo*-2-dibenzobicyclo[3.2.1]octadienol (41)** was prepared by hydrodemercuration of **40** in the usual fashion: mp 100–102 °C; ^{1}H NMR δ 6.7–7.6 (m, 8, aromatic H), 3.26 (d, 1, J = 4.5 Hz, H-1), 2.58 (d, 1, J = 11 Hz, H-8 syn), 2.25 (d of d, 1, J = 11, 4.5 Hz, H-8 anti), 1.17 (s, 3, bridgehead CH_3), and 1.46 ppm [s, 3, C(2) CH_3].

Oxymercuration of 19 in Acetone–Water. A solution of 0.70 g (3 mmol) of **19** and 2.87 g (9 mmol) of mercuric acetate in 50 ml of acetone–water (4:1) and 1.5 ml of glacial acetic acid was heated at reflux for 1 day. Addition of 1.0 g (47 mmol) of NaCl in 120 ml of water and extraction with chloroform was followed by the usual workup. The ^{1}H NMR spectrum showed a mixture of **25** and **26** in a 1:1 ratio.

Oxymercuration of 18 in Tetrahydrofuran–Water. A solution of 0.319 g (1 mmol) of mercuric acetate in 1.0 ml of water was added to a solution of 0.218 g (1 mmol) of **18** in 1.0 ml of tetrahydrofuran and the reaction mixture was stirred for 21.5 h. Reduction with sodium borohydride, followed by the usual workup, gave a mixture whose ^{1}H NMR spectrum showed about 17% **35** and 21% acetate **33**, with the remainder being alcohols **37** and **38**.

Oxymercuration of 20 in Aqueous Tetrahydrofuran. A solution of 0.70 g (3 mmol) of **20** and 1.45 g (4.5 mmol) of mercuric acetate in 30 ml of 50% aqueous tetrahydrofuran to which 1 ml of glacial acetic acid had been added was stirred for 2 h. NaOH (0.5 g) and excess sodium borohydride were added. After the usual workup, the ^{1}H NMR spectrum of the product showed only **20** and **41** in approximately a 1:1 ratio. No **30**, **31**, or **32** was observed.

Oxymercuration of 1 in Acetic Acid for a Short Time. A solution of 0.20 g (1 mmol) of **1** and 0.67 g (2 mmol) of mercuric acetate in 20 ml of glacial acetic acid was stirred for about 19 min before 1.0 g of NaCl was added. The solution was stirred for about 2 min before 100 ml of water was added. Sodium borohydride reduction gave a mixture whose ^{1}H NMR spectrum showed that approximately 30% of **1** had been converted to the acetate of **14**. No rearranged products were observed.

Oxymercuration of 20 in Acetic Acid–Water (4:1). A solution of 1.00 g (4.3 mmol) of **20** and 1.75 g (5.5 mmol) of mercuric acetate in 50 ml of glacial acetic acid–water (4:1) was stirred for 1 day before 2.0 g of NaCl was added. The precipitate was reduced with sodium borohydride. After the usual workup, a ^{1}H NMR spectrum of the product showed it to be exclusively the [3.2.1] alcohol **41**.

Oxymercuration of 20 in Acetic Acid–Methanol (4:1). A solution of 5.0 g (21.6 mmol) of **20** and 10.3 g (32.3 mmol) of mercuric acetate in 70 ml of an acetic acid–methanol (4:1) mixture was stirred for 15 h before 5.0 g (85 mmol) of NaCl was added. Workup as usual gave 7.7 g (70%) of *syn*-8-chloromercuri-*endo*-2,5-dimethyl-*exo*-2-dibenzobicyclo[3.2.1]octadienyl methyl ether (**44**), which, after recrystallization from chloroform–carbon tetrachloride, had mp 185–186°; ^{1}H NMR (Me_2SO-d_6) δ 6.7–7.0 (m, 8 H, aromatic H), 3.85 (d, 0.8 H, J = 4.5 Hz, H-1), 3.48 (s, 3 H, OCH_3), 3.05 (d, 0.7 H, J = 4.5 Hz, H-8 anti), 1.87 [s, 3 H, C(2) CH_3], and 1.95 ppm (s, 3 H, bridgehead CH_3).

Anal. Calcd for $C_{19}H_{19}OHgCl$: C, 45.69; H, 3.81. Found: C, 45.59; H, 3.73.

***endo*-2,5-Dimethyl-*exo*-2-dibenzobicyclo[3.2.1]octadienyl methyl ether (42)** was prepared by sodium borohydride reduction of **44**-Cl, oil: ^{1}H NMR δ 6.9–7.5 (m, 8, aromatic H), 3.51 (m, 1 H, J = 5 Hz, H-1), 3.38 (s, 3, OCH_3), 2.69 (d, 1, J = 11 Hz, H-8 syn), 2.20 (d of d, 1, J = 11, 5 Hz, H-8 anti), 1.75 [s, 3, C(2) CH_3], and 1.42 ppm (s, 3, bridgehead CH_3).

Oxymercuration of 20 in Acetic Acid–Methanol (19:1). A solution of 1.00 g (4.3 mmol) of **20** and 1.75 g (5.5 mmol) of mercuric acetate in 50 ml of acetic acid–methanol (19:1) was stirred for 1 day before 1.0 g of NaCl was added. Workup and sodium borohydride reduction gave a product whose ^{1}H NMR spectrum showed **42** (67%), **30** (22%), and **32** (11%).

Oxymercuration of 20 in Methanol. A solution of 2.1 g (9 mmol) of **20** and 4.35 g (13.5 mmol) of mercuric acetate in 35 ml of methanol was stirred for 17 h before 1.0 g (20 mmol) of NaCl and 75 ml of water were added. The precipitate was collected and dried in vacuo over P_2O_5, yielding 4.1 g of solid product. The ^{1}H NMR spectrum (Me_2SO-d_6) of the product mixture indicated that the [2.2.2] addition product had trans stereochemistry[32b] for the Hg–X and OCH_3 substituents [δ 4.27 ppm (J = 3 Hz, H-8)]. The ^{1}H NMR spectrum also indicated that the acetoxymercurials had been isolated, not the chloromercurials. To 4.0 g (7.6 mmol) of the product dissolved in 20

Table I. Oxymercuration of 1,4-Dimethyldibenzobicyclo[2.2.2]octatriene in Acetic Acid. Effect of Time on Product Composition

	Composition, %			
Time, h	20	28	29	28:29
0.25	56.4	24.9	18.7	57:43
0.50	47.2	28.2	24.6	53:47
1.0	27.9	38.9	33.3	54:46
2.0	22.7	48.8	28.5	63:37
4.5	14.7	54.2	31.1	64:36
9.0	11.8	65.5	24.7	72:28
21.0	12.5	72.3	15.2	83:17
32.5	9.7	77.0	13.3	85:15
44.5	10.8	75.6	13.6	85:15
66.5	9.9	80.1	10.0	89:11

ml of tetrahydrofuran and 20 ml of 2 M NaOH, 0.50 g (13.2 mmol) of sodium borohydride was added and the solution was stirred for 15 min. The solution was decanted from 1.49 g (92%) of metallic mercury and the usual workup gave 2.11 g (99%) of an oil. The ^{1}H NMR spectrum of the product mixture indicated that ethers **42** and **43** were present in approximately equal amounts. The ethers were separated by high-pressure liquid chromatography on silica gel with 4% ether in hexanes as elutant. The ^{1}H NMR spectrum of the second ether eluted corresponded with that of **42**. Recrystallization of the first fractions from hexane gave 1,4-dimethyl-7-dibenzobicyclo[2.2.2]octadienyl methyl ether (**43**): mp 107–108 °C; ^{1}H NMR δ 7.0–7.5 (m, 8, aromatic H), 3.38 (d of d, 1, J = 9, 3 Hz, H-7), 3.20 (s, 3, OCH_3), 2.07 (d of d, 1, J = 11, 9 Hz, H-8 anti), 2.00 [s, 3, C(1) CH_3], 1.93 [s, 3, C(4) CH_3], and 1.47 ppm (d of d, 1, J = 11, 3 Hz, H-8 syn).

Anal. Calcd for $C_{19}H_{20}O$: C, 86.36; H, 7.57. Found: C, 86.53; H, 7.66.

Stability of 29-OAc to Oxymercuration Conditions in Acetic Acid. Olefin **20** (2.32 g, 10 mmol) in 25 ml of glacial acetic acid was added to 3.18 g (10 mmol) of mercuric acetate in 25 ml of glacial acetic acid at room temperature. Aliquots (5.0 ml) were removed from time to time. NaCl (0.5 g) was added to each aliquot and 50 ml of water was added after 1–5 min of stirring. For the shorter reaction times, the time between NaCl addition and water addition was less. The solid product was then collected, washed with water, and dried on a suction filter. The ^{1}H NMR spectra (Me_2SO-d_6) of the resulting product mixtures were obtained and the product ratios were determined by comparing multiple integrations of the peaks at δ 6.52 (H-7 and H-8 of **20**) with those at 5.34 (d, J = 9 Hz, H-7 of **28**) and those at 4.48 ppm (d, J = 5 Hz, H-1 of **29**). Results are summarized in Table I.

Stability of 28-OAc to Oxymercuration Conditions in Acetic Acid. A solution of 1.40 g (6 mmol) of **20** and 3.83 g (12 mmol) of mercuric acetate in 25 ml of glacial acetic acid was stirred for 24 h and poured into 200 ml of water. The aqueous solution was decanted from the solid product and approximately 0.3 g of the product was dried in vacuo over P_2O_5. The remainder of the product was redissolved in 20 ml of glacial acetic acid and stirred for 17 h before 2.0 g (34 mmol) of NaCl was added. The solution was stirred for another 15 min, 100 ml of water was added, and the product was collected, washed with water, and dried. The ^{1}H NMR spectrum (Me_2SO-d_6) of the product (**28**-OAc) before its reaction with acetic acid indicated that no **20** or **29**-OAc were present. The ^{1}H NMR spectrum (Me_2SO-d_6) of the product after reaction in acetic acid also indicated no **20** or **29**-Cl.

1,4-Dimethyl-7-dibenzobicyclo[2.2.2]octadienol (55). To a solution of 10.0 g (43 mmol) of **20** and 7.45 g (197 mmol) of sodium borohydride in 110 ml of dry bis(2-methoxyethyl) ether (diglyme) at 0 °C, a solution of 10.5 ml (85 mmol) of boron trifluoride etherate in 40 ml of dry diglyme was added over a 2-h period under a nitrogen atmosphere. The reaction mixture was stirred for another 4 h during which the reaction was allowed to warm to room temperature. Water (25 ml) was *cautiously* added over 45 min, followed by 40 ml of 10% aqueous NaOH while the solution was cooled to 0 °C. To the solution, 40 ml of 30% hydrogen peroxide was added over a 30-min period and the reaction mixture warmed to room temperature and stirred for 13 h. Normal workup gave 10.6 g (98%) of **55**. Recrystallization from ethanol–water (1:1) gave 9.4 g (87%) of **55**: mp 144–145 °C; ^{1}H NMR δ 7.0–7.5 (m, 8, aromatic H), 3.75 (d of d, 1, J = 9, 3 Hz, H-7), 2.18 (d of d, 1, J = 13, 9 Hz, H-8 anti), 1.95 (s, 3, bridgehead CH_3), 1.88 (s, 3, bridgehead CH_3), and 1.22 ppm (d of d, 1, J = 13, 3 Hz, H-8 syn).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.40; H, 7.20. Found: C, 86.57; H, 7.29.

1,4-Dimethyl-7-dibenzobicyclo[2.2.2]octadienyl *p*-toluenesulfonate (56) was prepared from **55** and *p*-toluenesulfonyl chloride in dry pyridine at 0 °C. Workup and recrystallization from ether–petroleum ether (bp 60–70°) gave **56**: mp 89–91 °C dec; ^{1}H NMR δ 7.1–7.8 (m, 12, aromatic H), 4.62 (d of d, 1, J = 8, 3 Hz, H-7), 2.42 (s, 3, bridgehead CH_3), 2.12 (d of d, 1, J = 14, 8 Hz, H-8 anti), 1.87 (s, 6, bridgehead CH_3 and tosylate CH_3), and 1.53 ppm (d of d, 1, J = 14, 3 Hz, H-8 syn).

Anal. Calcd for $C_{25}H_{24}O_3S$: C, 74.26; H, 5.94. Found: C, 74.11; H, 6.06

Solvolysis of 56 in Acetic Acid with Sodium Acetate. Isolation of 2-Methylene-5-methyldibenzobicyclo[3.2.1]octadiene (32). A solution of 3.14 g (7.8 mmol) of **56** and 0.70 g (8.5 mmol) of sodium acetate in 60 ml of glacial acetic acid was heated at reflux for 12 h. The mixture was poured into 100 ml of benzene and 200 ml of water. Normal workup gave 1.8 g (100%) of olefin **32**, which after recrystallization from ethanol had mp 119–120°; ^{1}H NMR δ 6.9–7.75 (m, 8, aromatic H), 5.45 (s, 1 H, vinyl H cis to aromatic ring), 5.15 (s, 1 H, trans vinyl H), 4.00 (t, 1 H, J = 2 Hz, H-5), 2.37 (d, 2 H, J = 2 Hz, H-8), and 1.8 ppm (s, 3, CH_3).

Anal. Calcd for $C_{18}H_{16}$: C, 93.10; H, 6.90. Found: C, 93.22; H, 6.93.

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Registry No.—**1**, 2734-13-6; **18**, 58426-49-6; **19**, 58426-50-9; **20**, 58426-51-0; **21**, 58426-52-1; **26**, 2198-06-3; **28**-Cl, 58426-53-2; **28**-OAc, 58426-54-3; **29**-Cl, 58426-55-4; **29**-OAc, 58426-56-5; **30**, 58426-57-6; **32**, 58426-58-7; **34**, 58426-59-8; **35**, 58426-60-1; **36**, 58462-42-3; **40**-Cl, 58426-61-2; **41**, 58426-62-3; **42**, 58426-63-4; **43**, 58426-64-5; **44**, 58426-65-6; **47**, 58426-66-7; **48**, 58426-67-8; **49**, 2395-96-2; **50**, 58426-68-9; **51**, 58426-69-0; **52**, 781-43-1; **53**, 58426-70-3; **54**, 58426-71-4; **55**, 58426-72-5; **56**, 58426-73-6; *trans*-1,2-dichloroethene, 156-60-5; *cis*-1,2-dichloroethene, 156-59-2; mercuric acetate, 10507-39-8; 9-methylanthracene, 779-02-2.

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Bridged Polycyclic Compounds. 83. Steric and Bromine Substituent Acceleration in Bromination Reactions[1,2]

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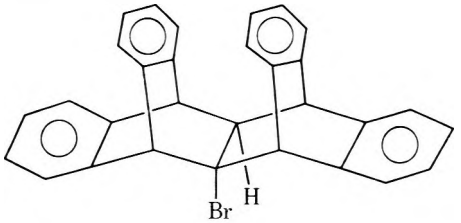
Free-radical brominations of a number of bridged compounds (compounds 3–9) have been carried out, with attention paid both to product compositions and to relative reactivities. Each of the compounds had at least one tertiary hydrogen atom at a nonbridgehead position, and reaction occurred exclusively at such positions. A solvent system was devised which scavenged hydrogen bromide rapidly, and competitive brominations were conducted with pairs of compounds. The relative reactivities of the compounds have been rationalized in terms of structural features, and the product compositions have also been discussed.

Some time ago it was reported[3] that 5a-bromojanusene (1) was more reactive toward free-radical bromination than



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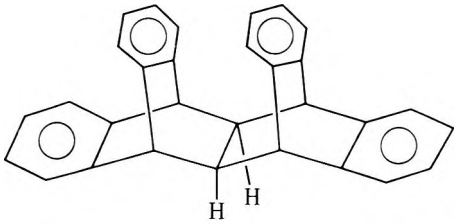

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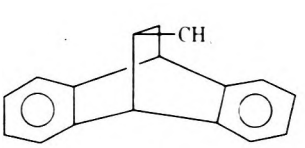
janusene (2) itself. This seemed to us to be an interesting result, as the usual explanation[4] for β-activation by bromine, that is, anti-neighboring group participation by bromine in the transition state for hydrogen abstraction, cannot be invoked in this case for obvious geometric reasons. Rather some syn activation process might be inferred, or the ring system itself, which is not without other unusual properties,[5] might be responsible for the rate enhancement. We therefore undertook the study reported in this paper to see whether or not such syn periplanar activation is a general phenomenon in the abstraction of tertiary hydrogen atoms by bromine atoms.

To this end, we determined to study the relative rates of free-radical bromination of compounds **3–9**. With these compounds we would be in a position not only to study the effect of bromine substituents upon the reactivities of vicinal hydrogen atoms, but also the effects of neighboring methyl groups.

Preparation of Reagents. 7-Methyldibenzobicyclo[2.2.2]octadiene (**3**)[6] and *cis*- (**4**)[7] and *trans*-7,8-dimethyldibenzobicyclo[2.2.2]octadiene (**5**)[7,8] had already been described. We found it convenient to prepare **4** and **5** by diene syntheses at 225 °C from anthracene and *cis*- and *trans*-2-



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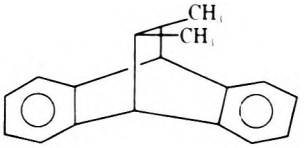

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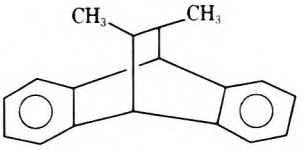

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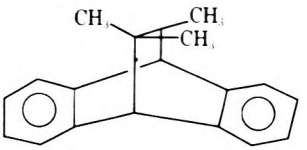

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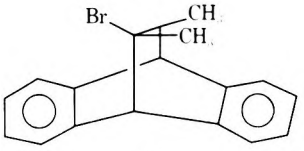

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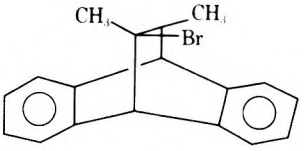

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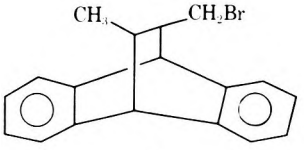

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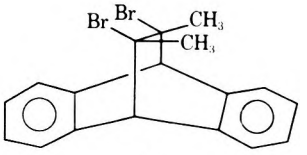

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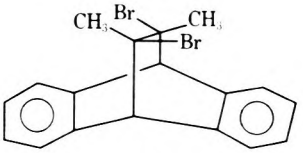

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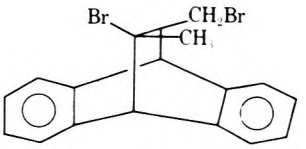

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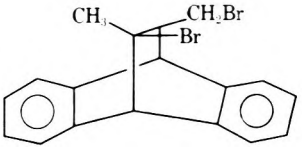

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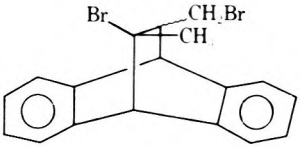

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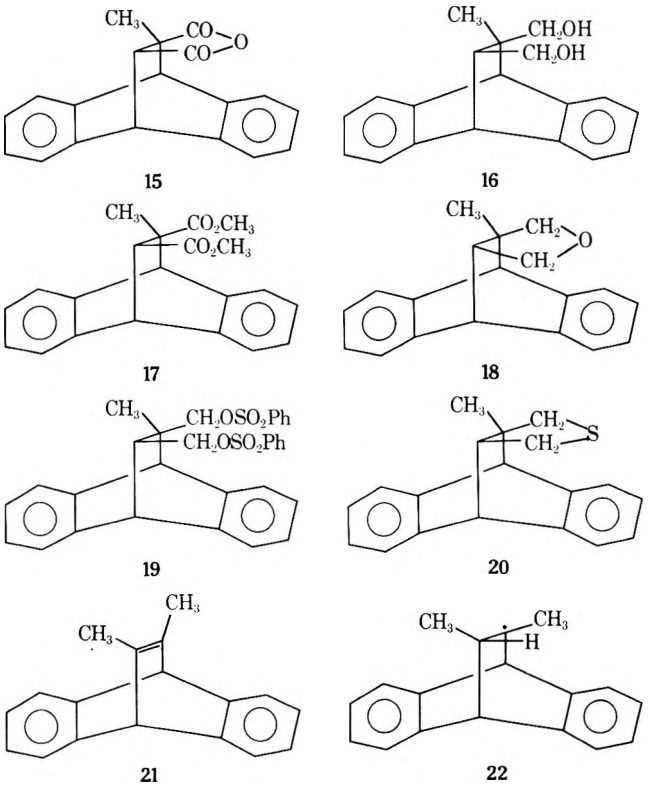
butene, respectively. When **4** was prepared in this fashion in a steel pressure autoclave, contamination with **5** was observed. This contamination, which was presumably the result of ferric ion catalyzed olefin isomerization, was eliminated by addition of small amounts of ethylenediaminetetraacetic acid and phthalonitrile to coordinate with the iron.

2-Methyl-2-butene could not be induced to react with anthracene to give **6**. Apparently the extra methyl group provides too much steric hindrance to allow reaction.[9] As **3**, **4**, and **5** had been prepared by lithium aluminum hydride reductive displacements on *p*-toluenesulfonate esters,[6-8] such a process appeared attractive for **6** as well. To this end, **16**, or its epimer, was required. Lithium aluminum hydride reduction of **15**[10] did not proceed well, but conversion of **15** to **17**,[10] followed by $LiAlH_4$ reduction, gave **16** readily



and in high purity. Attempts to convert the diol **16** to the bis-*p*-toluenesulfonate ester by standard procedures led instead to the tetrahydrofuran **18**, presumably by base-promoted reaction of the mono esters. The bisbenzenesulfonate ester **19** was prepared by oxidation of the readily prepared bisbenzenesulfinate ester.

Although the reduction of the analogue of **19** without the methyl group (and with *p*-toluenesulfonoxy groups) proceeds to give **4** in fair yield when special conditions are used, that of **19** led rather to the tetrahydrofuran **18**, presumably via attack at sulfur to give the monoester,[7] rather than at carbon to give the desired reduction product **6**. However, treatment of **19** with ethanolic sodium hydrosulfide gave the tetrahydrothiofuran **20**, which upon treatment with Raney nickel was readily converted to **6**.

The monobromo derivatives (**7** and **8**) of the dimethyl compounds were prepared by free-radical addition of hydrogen bromide to the olefin **21**. The trans isomer **8** predominated over the cis isomer **7** in a ratio of 7:1. Ionic addition of hydrogen bromide to **21** gave rearranged products with the dibenzobicyclo[3.2.1]octadiene skeleton, as well as [2.2.2] products. Attempts to prepare **7** and/or **8** by stereospecific syntheses failed. Although **7** and **8** were readily distinguished by ^1H NMR spectroscopy, the structures of these were not readily apparent from these data. X-Ray analysis of the major product (which was readily separated and purified) showed that it was the trans isomer **8**.

***trans*-7-Bromomethyl-8-methyldibenzobicyclo-[2.2.2]octadiene (9)** was prepared from the alcohol resulting from the reduction of the Diels–Alder adduct[12] of anthracene and methyl *trans*-crotonate. Treatment of this alcohol with triphenylphosphine dibromide gave **9**.

Methods of Competitive Bromination and Results. In order to measure the relative reactivities of the tertiary hydrogen atoms in the compounds of interest, we compared their rates of disappearance in paired sets[13] in photobromination reactions. Relative bromination rates will give relative hydrogen abstraction rates only if the reaction in eq 1

$$RH + Br\cdot \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\cdot + HBr \quad (1)$$

$$R\cdot + Br_2 \xrightarrow{k_2} RBr + Br\cdot \quad (2)$$

is irreversible, that is, $k_2[Br_2] \gg k_{-1}$ [HBr], or if k_{-1}/k_2 is identical for all of the alkyl radicals under study, which seems highly unlikely. Furthermore, the reverse reaction in eq 1 may lead to epimerization of **4** and **5** and of **7** and **8**. Indeed such epimerization may be used as a measure of reversibility. Thus, the high reactivity of the radical **22** from **4** with hydrogen bromide compared with bromine may be noted from the fact that treatment of **4** with 1 mmol of bromine in 60 mol of carbon tetrachloride give a mixture of 54% of **7** and **8**, 8–11% of **4**, and 31–33% of the trans isomer **5**.[14] Isomerization of **4** to **5** was reduced substantially when 4–6% of solvent was replaced by a hydrogen bromide scavenger, 2,3-epoxy-2,3-dimethylbutane, and was almost completely eliminated when ratios of 1 mol of **4**, 1 of Br_2, 50 of CCl_4, and 21 of epoxide were used (at 50% bromination, the hydrocarbon mixture contained 97% of **4** and 3% of **5**).

For preparative bromination reactions, we found that reversal and attendant isomerization could be lessened substantially by conducting the bromination in the presence of a water layer and using vigorous stirring. In this way the hydrogen bromide was extracted into the aqueous phase and its concentration in the organic solvent was low enough to cut down its competition with bromine for the intermediate radical.

Relative rates of disappearance were measured at 10–11 °C, using ratios of 0.5–1.0 mol of Br_2 to 1 of substrate mixture, 36 of CCl_4, and 21 of epoxide. After irradiation (tungsten lamp), solvents were removed by rotary evaporation, petroleum ether was added, and oxygen-containing substances were extracted with 85% phosphoric acid. Analysis was by ^1H NMR and/or GLC. Data and calculated relative reactivities are given in Table I and in Table II.

Discussion

When the data in Table I are corrected for the number of tertiary hydrogen sites, it becomes evident that the monomethyl derivative **3** and the trans dimethyl derivative **5** have a reactivity ratio of about 2, and the cis dimethyl compound **4** and the trimethyl compound **6** have one of about 1.5. These pairs differ in having a methyl group which might provide interference with the attacking bromine atom; this effect is small. Presumably in its attack on a hydrogen atom, the bromine atom is not greatly interfered with by the hydrogens of the syn methyl group. On the other hand, the relative reactivities of each tertiary site in **4** to that of **3** of 16:1, and the corresponding ratio of that in **6** to those in **5** of 30:1, show the relatively large rate enhancement caused by the additional eclipsed methyl group remote from the site of attack. We see no simple rationaliza-

Table I. Data and Results on Photobrominations in a Carbon Tetrachloride–2,3-Dimethyl-2,3-epoxybutane Mixture

Run	Mole ratios: Substrates	Mole ratios: Br_2	Recovered substrates,[a] % of aromatic peaks	Rel reactivity
1[b]	**5**, 0.55; **3**, 0.45	0.50	**5**, 45.0; **3**, 35.6	**3:5** = 1.2:1
2	**5**, 0.50; **3**, 0.50	0.88	**5**, 24.0; **3**, 24.0	**3:5** = 1.0:1
3	**4**, 0.63; **5**, 0.37	0.70	**4**, 6.4; **5**, 34.6	**4:5** = 34:1
4	**4**, 0.51; **5**, 0.49	0.94	**4**, 2.6; **5**, 45.	**4:5** = 35:1
5[b]	**5**, 0.52; **6**, 0.48	0.70	**5**, 48.2; **6**, 16.1	**5:6** = 14:1
6	**4**, 0.52; **6**, 0.48	0.59	**4**, 14.3; **6**, 32.4	**4:6** = 3.3:1
7[b,c]	**7**, 0.21; **8**, 0.74	0.79	**7**, 18.5; **8**, 23.0	**8:7** = 9.2:1
8[c]	**7**, 0.21; **8**, 0.74	0.87	**7**, 13.5; **8**, 5.0	**8:7** = 6.1:1
9[d]	**8**, 0.37; **6**, 0.61	0.24	**8**, 14.0; **6**, 44.0	**8:6** = 3.0
10[e]	**8**, 0.35; **6**, 0.63	0.30	**8**, 13.0; **6**, 46.0	**8:6** = 3.2
11[e]	**8**, 0.556; **9**, 0.418	0.59	**8**, 8.2; **9**, 41.0	**8:9** = 100:1[f]
12	**3**, 0.497; **9**, 0.503	0.53	**3**, 33.0; **9**, 46.5	**3:9** = 5.0:1

[a] Mixtures of bromides and/or dibromides were also present. [b] Run stopped before all bromine was consumed. [c] This sample contained 5% of an unknown impurity. [d] This sample also contained 2% of **7**. [e] This sample also contained 3% of **7**. [f] Value probably has high error; not used for Table II computation.

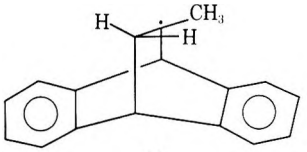
Table II. Relative Reactivities toward Bromine Atoms (Compound 5 ≡ 1.0)[a]

Compd	Rel reactivity	Rel reactivity per tertiary H atom
3	1.1	2.2
4	34.	34.
5	1.0	1.0
6	12.	24.
7	5.	10.
8	37.	74.
9	0.22	0.4[b]

[a] Estimated reliabilities ±0.25. [b] Assuming that one of the tertiary hydrogens is preferentially attacked.

tion of these results other than steric acceleration due to back-strain relief.[2]

Rate enhancement might be anticipated[16,17] when two groups compressed in the initial state move farther apart in the radical formed. As it may be assumed that the angles between groups at the radical site in these radicals (e.g., **22**, **23**, and **24**) will be greater than tetrahedral, steric acceleration should be noted when the transition state is sufficiently advanced along the reaction coordinate. Thus, as observed, **4** should react more rapidly than **3**, and **6** more rapidly than **5**.



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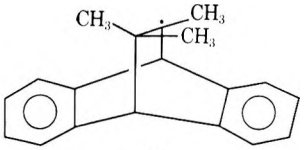

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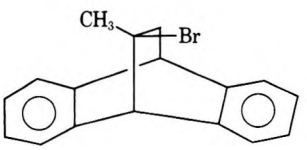

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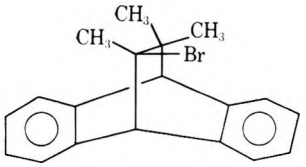

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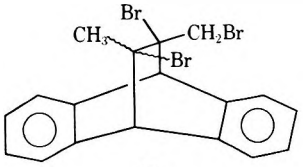
Steric acceleration of rate by back-strain relief has been noted by Simamura and Mayajima,[18] who observed that the tertiary equatorial hydrogen atom in 1,1,3,5-tetramethylcyclohexane reacts with alkylperoxy radicals 4.2 times as rapidly as the equivalent hydrogen atom in 1,3,5-trimethylcyclohexane, a result which was ascribed to relief of 1,3 interaction (methyl–methyl greater than methyl–hydrogen) in the hydrogen abstraction reaction. More recently, Abruscata and Tidwell[19] have ascribed the enhanced decomposition rate of *tert*-butyl di-*tert*-butylperoxyacetate over that of *tert*-butyl peroxyisobutyrate to back-strain relief. These cases, plus those discussed in this paper, put the steric acceleration phenomenon upon a solid base.

The products of bromination of **3** and **6** were, as anticipated, those of reaction at the tertiary site, **25** from **3** and **26** from **6**. Although one might anticipate that the product mixtures from **4** and **5** would be identical, as they both arise from the common radical **22**, this is not the case, for straightforward reasons. As is noted below and in Table II, bromides **7** and **8**, which have somewhat different reactivities (**8** > **7**), are both significantly more reactive than the trans-dimethyl compound **5**, and **8** is also more reactive than the cis-dimethyl compound **4**. This means that when bromination of **4** and **5** are conducted under conditions where substantial bromination occurs, the primary products **7** and **8** are further consumed to give dibromides **10** and **11** and the observed product ratio of **7**:**8** is the result of a complicated composition of formation and disappearance rates. Our data were not precise enough (nor did we conduct experiments of small enough reaction) to enable us to give relative rates of capture of **22** with any degree of precision. However, as may be anticipated from the data in Table II, when **5** was brominated extensively, the product mixture contained much dibromide, some **7**, and only traces of **8**.[20] On the other hand, when the more reactive **4** was brominated, much monobromide was observed in the product with ratios of **8**:**7** as high as 1.[20] This suggests that **22** is not highly discriminating in its reaction with bromine, and that in the transition state for its reaction to give **7**, the steric strain which results between the two eclipsing methyl groups and the hydrogen atom and the entering bromine atom is roughly equal to that in the transition state leading to **8**, resulting from eclipsing strains between methyl and hydrogen and methyl and the entering bromine atom. As no large dipoles are involved, and as bromine and methyl have approximately equal steric requirements,[21] this result appears reasonable. An amusing consequence of the difference between the sizes of hydrogen and bromine substituents is the large difference in the rates of formation of **22** from **4** and **5** and the small difference in the rates of reaction of **22** to give **7** and **8**, processes that appear, without consideration of steric interactions between leaving, entering, and remaining groups, to be almost alike. It would be

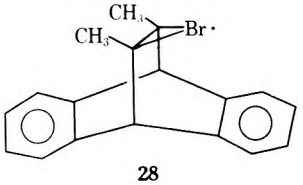
useful to check these ideas by bromine abstraction from **7** and **8** with a small radical reagent. These should have very similar reactivities.

Bromination of Monobromo Compounds. The bromination of **7** and **8**, or the bromination of **4** and **5**, led to mixtures of **10** and **11** in which one isomer predominated (7:1). The principal isomer was readily purified; x-ray analysis showed it to be the trans isomer **11**.

The product from photobromination of **9** was a mixture of the diastereoisomeric monobromination products **12** and **13** and of the dibromination products **27**. None of the



27



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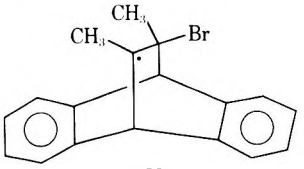

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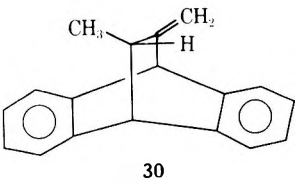

30

monobromination products **14** (which would result from attack on the tertiary hydrogen atom next to the bromomethyl group) was noted, although attempts to observe it (by ^1H NMR analysis, obviously an inprecise tool) in product mixtures were made. Whether this means that the **14** formed was so reactive that it led quantitatively to **27** or, as we feel more likely,[22] little was formed and **27** came largely from **12** and/or **13**, is not clear. Even if all of the **27** came from **14** it represented less than the amount of **12** and **13** and thus the other tertiary hydrogen was more reactive than that geminal to the bromomethyl group.

As described in the introduction to this paper, our studies were undertaken to see whether the rate enhancement noted with bromojanusene (**1**) over janusene (**2**) was a general phenomenon of syn-periplanar activation in the attack on hydrogen by bromine atom.[23] As the data in Tables I and II show, such expectations were not realized. Thus **7** is only one-third as reactive per hydrogen atom as **4**, rather than more reactive. If one, however, accepts the premise[24] that the inductive effect of a vicinal bromide should reduce reactivity by a factor of 7–9, it would appear that the net reduction is made of a slight increase of the sort apparent in **1** coupled with the inductive decrease. The effect of adding a bromine substituent in the trans-dimethyl compound **5** may be seen in the relative reactivities of **5**, **8**, and **9**. In comparing **8** and **5**, we see, rather than the anticipated[24] loss of reactivity by a factor of 7–9, an increase in reactivity by a factor of 74. We have noted above that the location of a methyl group in the position remote from the site of attack which eclipsed the methyl group in **5** (i.e., to give **6**) increases the reactivity by a factor of 34, and we have ascribed this rate enhancement to steric acceleration. As the effect of bromine–methyl eclipsing in **8** is probably similar to that of the two eclipsed methyl groups in **6** (or in **8**), a portion of the rate enhancement must be due to steric acceleration of rate. However, this cannot be the sole factor, as there still remains the fact that **8** is seven times as reactive as **7**.

It has been suggested[4] that there is anchimeric assistance by vicinal bromine in bromine atom attack on β-hydrogen atoms, and evidence favoring this idea continues to accumulate.[24,25] For this activation to operate most effectively, an anti-periplanar relationship between the activating bromine atom and the hydrogen atom is believed[24b] to be required. Under such conditions, activation of over 100 times is noted (and with correction for inductive effect, the activation may be computed[24b] to be about 10^3). It is known[26] in ionic systems that anchimeric assistance is reduced or eliminated when the steric relationship between groups is changed from the antiperiplanar relation (dihedral angle of 180°) to that of trans groups in the bicyclo[2.2.2]octadiene system (dihedral angle of 120°), and a similar effect should[24b] be noted in radical reactions. Thus the relatively small factor of 7 between **8** and **7** seems consistent with a transition state leading to **28** rather than to the open radical **29** in the reaction of **8** with a bromine atom.[27]

While the steric acceleration component of the rate enhancements is a ground-state effect (in the sense that it is relief of ground-state strain that affects reactivities), the remaining effect, anchimeric assistance, is one arising in the transition state differences between **8** giving **28** (and **29**) and **7** giving **29**. The **28** ⇄ **29** equilibrium and their relative reaction rates with molecules (with hydrogen bromide to give **7** from **29** and **8** from **28** and **29**, and with bromine to give **10** from **29** and **11** from **28** and **29**) which pass over similar transition states might show similar phenomena. Indeed this is true. Thus the photobrominations of **7** and/or **8** give **11** and **10** in a ratio of about 7:1, quite similar to the ratio of reactivities of **8** and **7**. Free-radical addition of hydrogen bromide to **21**, which involves bromine atom addition to give the **28** ⇄ **29** mixture, then hydrogen transfer to give **7** and **8**, forms these two substances in a 1:7 ratio. These results may be compared with those involving the radical **22** where hydrogen removal to form **22** and bromine transfer to **22** differ considerably in selectivity.

The results with the trans methyl bromomethyl compound **9** (reactivity 40% of that of the trans dimethyl compound **5**, reaction largely geminal to methyl to give **12** and **13** rather than geminal to bromomethyl to give **14**, and substantial amounts of dibromination) are consistent with the concepts outlined above. The reactivity fits that[24b] of a hydrogen γ to a bromine atom exactly (depression due to the inductive effect), and lack of the reaction at the tertiary proton geminal to the bromomethyl group indicates the extra depression of β-bromo substituent when no anchimeric assistance is seen. Presumable causes might be conformational difficulties, or deactivation by intramolecular complexing with the aromatic ring. The reactivities to be anticipated for **12**, **13**, or **14** compared with **9** (as judged by those of **7** and **8** compared with **5**) make understandable the fact that substantial amounts of dibromination are seen in the bromination of **9**.

Russell and Brown[28] have reported that a heterolytic dark reaction may occur with tertiary-alkyl halides. In order to show that such a reaction path did not compete in our systems, we held solutions of bromine, **7**, and **8** in carbon tetrachloride in the dark at reflux for 2 h or at room temperature for 1 day. No **10** or **11** was produced; instead partial rearrangements to bromo derivatives of dibenzobicyclo[3.2.1]octadiene were observed. An alternative path for bromination involving hydrogen bromide elimination–bromine addition[29] was also considered. However, addition of bromine to **21** (one of the possible elimination products from **7** or **8**) gave no **10** or **11**; again only [3.2.1] rearrangement–addition was observed.[20] Similarly **30** (anticipated elimination product from **9** or possibility from **7** or **8**) gave none of the products observed in the photobromination.[20] Hence the two paths may be disregarded.

Experimental Section

***trans*-7,8-Dimethyldibenzobicyclo[2.2.2]octadiene (5).** A 0.5-l. steel autoclave was cooled with dry ice and charged with 35 g (0.21 mol) of anthracene, 0.5 g of 4-*tert*-butylcatechol, 200 g of dry

ice cooled *m*-xylene, and 100 ml (1.5 mol) of liquid *trans*-2-butene (Phillips). The autoclave was closed and allowed to warm to room temperature. It was then placed in a heating jacket and kept at 220–230 °C for 6 days. The vessel was then cooled to room temperature, the gases vented, and the *m*-xylene removed almost completely by rotary evaporation. The crude solids were then dissolved in petroleum ether (bp 60–70 °C), and shaken three times with concentrated sulfuric acid, one time each with water, aqueous sodium bicarbonate, and again with water. This sulfuric acid treatment makes unnecessary the usual method of removing unreacted anthracene by reacting it with maleic anhydride and dissolving that adduct by boiling in aqueous sodium hydroxide. The solution was dried, filtered, and concentrated. Recrystallization from petroleum ether gave 36 g (76%) of **5**: mp 93–94 °C (lit.[7,8] 89–92 °C); ^{1}H NMR (CCl_4) δ 0.8 (d, J = 6 Hz, 6 H, CH_3), 1.3 (m, 2 H, H-7 and -8), 3.82 (d, J = 1.5 Hz, 2 H, H-1 and -4), 7.2 (m, 8 H, aromatic H).

***cis*-7,8-Dimethyldibenzobicyclo[2.2.2]octadiene (4)** was prepared in a similar fashion (on anthracene = 40 g scale) except that *cis*-2-butene was used and 2 g of ethylenediaminetetraacetic acid and 2 g of phthalonitrile were added to avoid ferric ion catalyzed olefin isomerization. Recrystallization from petroleum ether gave 31.7 g of **4** (60%): mp 172–173.5 °C (lit.[7] 173–174 °C); ^{1}H NMR (CCl_4) δ 0.65 (d, J = 6 Hz, 6 H, CH_3), 2.03 (m, 2 H, H-7 and -8), 3.82 (d, J = 1.5 Hz, 2 H, H-1 and -4), 7.2 (m, 8 H, aromatic H).

***cis*-7,8-Bis(hydroxymethyl)-7-methyldibenzobicyclo[2.2.2]-octadiene (16).** A solution of 23.4 g (0.070 mol) of **17**[10] in 130 ml of dry tetrahydrofuran (THF) was added rapidly with stirring to a solution of 4.75 g (0.12 mol) of lithium aluminum hydride in 200 ml of THF. The reaction mixture was heated at reflux for 3 h, then cooled and poured onto ice. Workup by careful acidification, ether extraction, evaporation of solvent, and recrystallization from ethyl acetate gave 17.3 g (88%) of **16**: mp 146–148.5 °C; ^{1}H NMR ($CDCl_3$–D_2O) δ 0.88 (s, 3 H, CH_3), 1.75 (m, J = 9.3, 5, 2 Hz, 1 H, H-8), 3.05–3.72 (m, 5 H), 4.02 (d, J = 2 Hz, 1 H, H-4), 7.16 (m, 8 H, aromatic H).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.61; H, 7.20.

7-Methyl-7,8-oxydimethyldibenzobicyclo[2.2.2]octadiene (18). Treatment of **16** with *p*-toluenesulfonyl chloride and tri-*n*-butylamine under standard[30] conditions for the preparation of *p*-toluenesulfonate esters led instead to excellent yields of **18**: mp 133.5–135 °C; ^{1}H NMR (CCl_4) δ 0.93 (s, 3 H, CH_3), 2.06 (m, J = 5.1, 3, 1.5 Hz, 1 H, H-8), 3.02–3.98 (m, 6 H), 7.08 (m, 8 H, aromatic H).

Anal. Calcd for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.93; H, 6.99.

***cis*-7,8-Bis(benzenesulfonoxymethyl)-7-methyldibenzobicyclo[2.2.2]octadiene (19).** A saturated solution of 2 g (7.2 mmol) of **16** in anhydrous ether was prepared at 0 °C and 1.1 g (14 mmol) of pyridine was added. Benzenesulfinyl chloride[31] (2.8 g, 16 mmol) was added slowly at 0 °C, and the resulting mixture was kept in a refrigerator overnight. The solid (pyridine hydrochloride) was filtered, and the ethereal solution was washed with dilute acid, dilute base, and water. The solution was dried ($MgSO_4$) and then evaporated to dryness. The resulting mixture of diastereoisomers was oxidized to the sulfonate ester **19** with *m*-chloroperbenzoic acid using the general procedure of Wilt, Stein, and Wagner.[32] Recrystallization from ethyl acetate gave pure **19**: mp 147–148 °C; ^{1}H NMR ($CDCl_3$) δ 0.8 (s, 3 H, CH_3), 1.27 (m, 1 H, H-8), 3.2–4.05 (m, 5 H), 4.16 (d, J = 2 Hz, H-4), 7–8 (m, 18 H, aromatic H).

Anal. Calcd for $C_{31}H_{28}O_6S_2$: C, 66.41; H, 5.03. Found: C, 66.58; H, 4.96.

7-Methyl-7,8-thiodimethyldibenzobicyclo[2.2.2]octadiene (20). Small slivers of sodium (1.65 g, 7.1 mmol) were added to 100 ml of anhydrous ethanol in a 250-ml, two-neck, round-bottom flask. Anhydrous hydrogen sulfide was bubbled through this medium until saturation. About 3.8 g (7.2 mmol) of **19** (which was dried by evaporating the benzene from its benzene solution) was then washed into this reaction medium using a minimum of anhydrous ethanol. The solution was refluxed for 3 days, using a condenser fitted with a $CaSO_4$ drying tube. The solution was poured into ether and washed with portions of water, aqueous sodium carbonate, and water. The ether layer was dried ($MgSO_4$). Evaporation of the ether left **20**, possibly contaminated with traces of **18**. Recrystallization from absolute ethanol gave **20**: mp 154–155 °C; ^{1}H NMR (CCl_4) δ 1.03 (s, 3 H, CH_3), 2–2.8 (m, 5 H, H-8, $-CH_2S$), 3.81 (s, 1 H, H-1), 3.90 (d, J = 2 Hz, 1 H, H-4), 7.1 (m, 8 H, aromatic H).

Anal. Calcd for $C_{19}H_{18}S$: C, 81.97; H, 6.52. Found: C, 81.86; H, 6.52.

7,7,8-Trimethyldibenzobicyclo[2.2.2]octadiene (6). About 1.2 g of the crude thioether **20** was added under nitrogen to an excess of W-7 Raney nickel[33] in 100 ml of anhydrous ether. Stirring was continued at reflux under nitrogen for 3 h. The nickel (caution! pyrophoric) was removed by filtration through a fritted glass funnel. After the solvent was evaporated, the residue was dissolved in petroleum ether and washed twice with dilute HCl, once with dilute $NaHCO_3$, and then with water. Any cyclic ether **18** was removed by extraction with concentrated H_2SO_4 before the other extractions. Recrystallization by evaporation of the petroleum ether gave pure **6**: mp 89.5–90 °C; ^{1}H NMR (CCl_4) δ 0.61 (s, 3 H, CH_3), 0.76 (d, J = 7.3 Hz, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 1.6 (m, J = 7.3, 2 Hz, 1 H, H-8), 3.6 (s, 1 H, H-1), 3.79 (d, J = 2 Hz, 1 H, H-4), 7.1 (m, 8 H, aromatic H).

Anal. Calcd for $C_{19}H_{20}$: C, 91.88; H, 8.12. Found: C, 91.71; H, 8.08.

***trans*-7-Bromomethyl-8-methyldibenzobicyclo[2.2.2]octadiene (9).** A solution of 40 g (0.16 mol) of *trans*-7-hydroxymethyl-8-methyldibenzobicyclo[2.2.2]octadiene[7] and 420 g (1.6 mol) of triphenylphosphine in 400 ml of dry dimethylformamide was placed in a three-necked flask covered with foil to prevent light from entering. After deaeration with nitrogen, 256 g (1.6 mol) of bromine was added dropwise, with the temperature controlled to below 100 °C. Stirring, nitrogen bubbling, and heating at 90 °C were continued for 5 days. The mixture was then cooled and poured into water. Ether extraction, solvent evaporation, partial dissolution in carbon tetrachloride, and filtration gave a solution of **9** and triphenylphosphine oxide and a solid residue of the oxide. The solution was dried ($CaSO_4$) and the solvent distilled off. The residue was chromatographed on silica gel (1 kg, 60–200 mesh) using petroleum ether–benzene mixtures to elute **9** and retain the oxide. **9** was contaminated with **21** and with 7-methylene-8-methyldibenzobicyclo[2.2.2]octadiene (**30**). Eluted fractions rich in **9** were dissolved in *n*-hexane, shaken with concentrated sulfuric acid, and recrystallized from *n*-hexane. The **9** had mp 88.5–89 °C; ^{1}H NMR (CCl_4) δ 0.78 (d, J = 6.5 Hz, 3 H, CH_3), 1.94 (m, 2 H, H-7 and -8), 3.15 (m, 2 H, CH_2Br), 3.82 (d, J = 2 Hz, 1 H, H-4), 4.3 (d, J = 2 Hz, 1 H, H-1), 7.13 (m, 8 H, aromatic H).

Anal. Calcd for $C_{18}H_{17}Br$: C, 69.02; H, 5.47. Found: C, 69.01; H, 5.60.

7-Methylene-8-methyldibenzobicyclo[2.2.2]octadiene (30). Compound **30**-enriched fractions of the chromatographed products obtained in the synthesis of **9** were fractionally recrystallized from absolute ethanol until pure **30** was obtained. An analytical sample of **30** had mp 98–98.5 °C; ^{1}H NMR (CCl_4) δ 0.88 (d, J = 7 Hz, 3 H, CH_3), 2.52 (m, 1 H, H-8), 4.6 (m, 2 H, CH_2), 3.98 (d, J = 2.5 Hz, 1 H, H-4), 5.06 (d, J = 2.3 Hz, 1 H, H-1), 7.08 (m, 8 H, aromatic H).

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.13; H, 6.98.

***trans*-7,8-Dibromo-7,8-dimethyldibenzobicyclo[2.2.2]octadiene (11).** This compound was prepared by photobromination of either **4** or **5** of a mixture of these. The reaction proceeded badly when conducted in the normal fashion (addition of bromine to **4** or **5** in CCl_4), because of the presence of hydrogen bromide which interfered with the reaction of intervening radicals with bromine. The following technique, in which water was used to scavenge the hydrogen bromide, gave good yields of dibromides from which **11** was readily recovered.

A solution of 10 g (0.043 mol) of **5** (**4** may be used equally well) in 500 ml of CCl_4 and 1200 ml of water was placed in a 2-l. three-neck round-bottom flask fitted with a mechanical stirrer and a dropping funnel. The flask was cooled to 10 °C and irradiated with a 1000-W incandescent light bulb. Bromine (6.9 g, 0.043 mol) was added in three portions, with vigorous stirring of the two-phase system and changing the water before each addition, made after the bromine color had substantially faded. The product mixture was investigated by ^{1}H NMR; if conversion to **11** and **10** was less than 95%, additional bromine was added. The ^{1}H NMR spectrum indicated that the ratio of **11**:**10** was about 7:1, and initial fractional recrystallization from petroleum ether and final recrystallization by solvent evaporation from CCl_4 gave **11**: mp 153–154.5 °C; ^{1}H NMR (CCl_4) δ 1.99 (s, 6 H, CH_3), 4.47 (s, 2 H, H-1 and 4), 7.18 (m, 8 H, aromatic H).

Anal. Calcd for $C_{18}H_{16}Br_2$: C, 55.13; H, 4.11. Found: C, 55.26; H, 4.24.

***cis*-7,8-Dibromo-7,8-dimethyldibenzobicyclo[2.2.2]octadiene (10)** was not isolated from the reaction mixture but its ^{1}H NMR spectrum was inferred from those of enriched mixtures from

the preparation of the trans isomer: ^{1}H NMR (CCl_4) δ 1.77 (s, 6 H, CH_3), 4.47 (s, 2 H, H-1 and 4), 7.18 (m, 8 H, aromatic H).

7,8-Dimethyldibenzobicyclo[2.2.2]octatriene (21). To a mixture of 2.6 g (0.042 mol) of zinc powder, 0.5 ml of glacial acetic acid, 2 g of ethylenediaminetetraacetic acid, and 300 ml of anhydrous ether in a 500-ml round-bottom flask equipped with a reflux condenser, 6.5 g (0.017 mol) of **10** and **11** (saturated solution in ether) was added with stirring at a rate which sustained gentle reflux. After addition was complete, stirring at reflux was continued for 2 h. The solids were removed by suction filtration, and the solution was washed with water and dried ($MgSO_4$). Evaporation of the ether left almost pure **21**, which after recrystallization from 95% ethanol had mp 189.5–190.5 °C; ^{1}H NMR (CCl_4) δ 1.8 (s, 6 H, CH_3), 4.58 (s, 2 H, H-1 and -4), 6.99 (symmetrical m, 8 H, aromatic H).

Anal. Calcd for $C_{13}H_{16}$: C, 93.06; H, 6.94. Found: C, 92.89; H, 7.13.

7-Bromo-*trans*-7,8-dimethyldibenzobicyclo[2.2.2]octadiene (8). A solution of 1 g (4.3 mmol) of **21** in purified *n*-hexane was cooled to 0 °C and placed in a quartz tube fitted with an inlet tube placed into the solution and a reflux condenser. The tube was irradiated with a GE H-100-A-4T lamp from which the glass envelope had been removed and 13 g (0.16 mol) of anhydrous hydrogen bromide was bubbled through the ice-cold solution over a 50-min period. After the addition, the excess hydrogen bromide was flushed out by air or nitrogen bubbling and the ultraviolet light then turned off. The hexane solution was washed with water and the solvent evaporated. A ^{1}H NMR spectrum indicated that the residue was a mixture of **8** and **7** in a 7:1 ratio, respectively. Fractional recrystallization from petroleum ether, followed by solvent evaporation from carbon tetrachloride, gave **8**: mp 95–102 °C dec; ^{1}H NMR (CCl_4) δ 1.03 (d, J = 7 Hz, 3 H, CH_3-8), 1.65 (s, 3 H, CH_3-7), 1.72 (m, J = 7, 2 Hz, 1 H, H-8), 3.85 (d, J = 2 Hz, 1 H, H-4), 4.39 (s, 1 H, H-1), 7.1 (m, 8 H, aromatic H).

Anal. Calcd for $C_{18}H_{17}Br$: C, 69.02; H, 5.47. Found: C, 69.04; H, 5.35.

7-Bromo-*cis*-7,8-dimethyldibenzobicyclo[2.2.2]octadiene (7). Attempts to separate pure **7** from the **7**–**8** mixture described above were not successful. However, its ^{1}H NMR spectrum was inferred from enriched mixtures: ^{1}H NMR (CCl_4) δ 0.89 (d, J = 7 Hz, 3 H, CH_3-8), 1.48 (s, 3 H, CH_3-7), 2.72 (m, J = 7, 2 Hz, 1 H, H-8), 3.8 (d, J = 2 Hz, 1 H, H-4, 4.35 (s, 1 H, H-1), 7.1 (m, 8 H, aromatic H).

Photobromination of *trans*-8-Bromomethyl-7-methyldibenzobicyclo[2.2.2]octadiene (9). In order to decipher the reaction path of the photobromination of **9**, we treated **9** with bromine at 20 °C on a small scale exactly as described for the competitive reactions. On a larger scale the two-phase method, with water as hydrogen bromide scavenger, described for the preparation of **25** and **26** proved quite useful. Difficulty in separation of products prompted us to rely entirely on ^{1}H NMR spectroscopy for product identification and estimation. Only three groups of ^{1}H NMR product peaks were noted, even when reactions were carried out to different extents or when enriched fractions were prepared by crystallizations. The chemical shifts, splitting patterns, and intensities of these groups of peaks allow the following assignments.

(*E*)-7-Bromo-8-bromomethyl-7-methyldibenzobicyclo[2.2.2]octadiene (12): ^{1}H NMR (CCl_4) δ 1.48 (s, 3 H, CH_3), 2.5–4 (m, 3 H, CH_2Br and H-8), 4.3 (s, 1 H, H-1), 4.55 (d, J = 2 Hz, 1 H, H-4), ~7.1 (m, 8 H, aromatic H).

(*Z*)-7-Bromo-8-bromomethyl-7-methyldibenzobicyclo[2.2.2]octadiene (13): ^{1}H NMR (CCl_4) δ 1.65 (s, 3 H, CH_3), 2.5–4 (m, CH_2Br and H-8), 4.4 (s, 1 H, H-1), 4.62 (d, J = 2 Hz, 1 H, H-4), ~7.1 (m, 8 H, aromatic H).

7,8-Dibromo-7-bromomethyl-8-methyldibenzobicyclo[2.2.2]octadiene (27): ^{1}H NMR (CCl_4) δ 2.0 (s, 3 H, CH_3), 3.3 (d, J = 11.6 Hz, 1 H, CH_2Br), 3.9 (d, J = 11.6 Hz, 1 H, CH_2Br), 4.5 (s, 1 H, H-4), 5.05 (s, 1 H, H-1), 7.25 (m, 8 H, aromatic H).

The *E*–*Z* assignment of **12** and **13** must be considered tentative at present. The chemical shifts of the 3 H singlets at 1.48 and 1.65 are strikingly similar to the methyl groups next to the bromines in **8** and **7**, respectively, and this forms the basis for the geometric assignment of **12** and **13**. The methyl group in compound **14** is expected to be a doublet at higher field. The structure of **12** and **13** is confirmed by the 1 H singlet in the bridgehead region with their chemical shifts being very close to the comparable ones of **7** and **8**. The required 1 H doublet bridgehead hydrogens are at surprisingly low fields when compared to the analogous hydrogens in **9**. The nonresolvable multiplets at δ 2.5–4 are to be expected for the single bridge hydrogen and two diastereotopic hydrogens (CH_2Br) which are coupled with each other. Compounds **14** would give rise to resolvable twin doublets for the diastereotopic hydrogens which could only be coupled with each other as in the case of **27**.

The product **27** has the expected two doublets which are characteristic of diastereotopic methylene hydrogens. The methyl group and bridgehead hydrogens should give rise to singlets as observed. The methyl singlet has the identical frequency as the methyl hydrogens in **11**.

The compounds **12**, **13**, **27**, and **9** accounted for more than 90% of the aromatic peaks for the scavenged reactions carried out to 50% completion at room temperature.

Competitive Brominations. Most of the necessary details are given in the discussion section and in Table I. The percentages of substrates which were recovered after reaction were determined by dividing the integration per hydrogen of their singlet or doublet bridgehead or methyl ^{1}H NMR peaks (Varian A60-A) by the integration per hydrogen of the aromatic peak total. The product percentages were determined in like manner to serve as a check, and there was agreement within the normal experimental error (±3%) of such ^{1}H NMR techniques. Although the total percent of remaining **4** and **5** was determined in this way, GLC (5 ft × 0.125 in. SE-30 column, 150 °C) had to be used in obtaining their ratio. As GLC did not separate **4** and **5** from their bromide products, the latter had to be removed prior to injection. This was accomplished by treatment of the entire reaction mixture with refluxing ethanolic silver nitrate, subsequent evaporation of the solvent, dissolution in petroleum ether and aqueous ammonia, and extraction of the organic layer with concentrated sulfuric acid. The ratio of **5** to **6** could similarily be determined by GLC and was used as a check on the ratio obtained directly from 60-MHz ^{1}H NMR spectra. The ratio of **7** to **8** was not obtainable from 60-MHz ^{1}H NMR spectra either. However, the doublet methyl as well as singlet bridgehead hydrogen peaks were completely separated in 100-MHz ^{1}H NMR (Jeolco PFT-100) spectra. Integration by the cut-and-weigh method afforded the desired ratio.

X-Ray Analyses. As we were unable to prepare **7**, **8**, **10**, or **11** by stereospecific syntheses, and spectroscopic data were ambiguous, x-ray structure analysis was conducted on one of the isomers of each pair. In both cases the isomer used for the analysis was the one which predominated in the preparations and had methyl groups shifted downfield in its ^{1}H NMR spectrum from those in the spectrum of the isomer that could not be isolated. The x-ray analysis showed that the major isomers were **8** and **11**.

Crystal Data on 7-Bromo-*trans*-7,8-dimethyldibenzobicyclo[2.2.2]octadiene (8). X-Ray crystal structure analysis of this compound was undertaken in order to determine whether the methyl groups were in the cis or trans configuration. The crystals were obtained from petroleum ether–carbon tetrachloride solution by evaporation. They grew as colorless, transparent needles.

The unit cell was found to be monoclinic with dimensions (standard deviations in parentheses) a = 10.640 Å (σ = 0.006 Å); b = 9.401 Å (σ = 0.003 Å); c = 29.133 Å (σ = 0.012 Å); β = 95.84° (σ = 0.04°). The observed density was 1.43 g/cm^3. Assuming eight molecules of $C_{18}H_{17}Br$ per unit cell gives a calculated density of 1.44 g/cm^3. Thus the cell contains eight molecules. Systematically absent spectra were ($h0l$) with l odd and ($0k0$) with k odd. The space group therefore is $P2_1/c$. Within the limiting sphere of Cu Kα radiation there lie 6100 independent reflections. Measurements were made of the intensities of all reflections for which $2\theta \leq 118°$. Of the 4472 in this category only 2516 with intensities exceeding three times background were used in the analysis. The crystal used in the intensity measurements was 0.2 × 0.25 × 0.3 mm. No absorption correction was applied [μ(Cu Kα) = 41.05 cm^{-1}]. The data were collected using a Syntex P$\bar{1}$ diffractometer in the θ–2θ scan mode, with a scanning rate of 2 deg/min. The Cu Kα line was selected using a graphite crystal monochromator.

Structure Determination. The space group $P2_1/c$ has a multiplicity of four and so the asymmetric unit contains two molecules of $C_{18}H_{17}Br$. The coordinates of the two bromine atoms were determined from an unsharpened three-dimensional Patterson synthesis. A three-dimensional electron density distribution, calculated using the bromine phases only, gave immediately the positions of the carbon atoms (reliability index, R = 0.44). Fourier refinement of the structure converged at R = 0.32. Further refinement was carried out by the block-diagonal least-squares procedure with unit weights and individual isotropic thermal parameters. The least-squares refinement converged at R = 0.17. At this point it was clear that the two methyl groups were in the trans configuration and the analysis was terminated.

The atomic coordinates of the two crystallographically indepen-

Table III. Fractional Coordinates (× 10^4) and Isotropic Thermal Parameters (× 10^3) Defining the Crystal Structure of 7-Bromo-*trans*-7,8-dimethyldibenzobicyclo[2.2.2]octadiene[a]

Atom	x	y	z	u
Br1A	422 (3)	2649 (4)	3501 (1)	101 (1)
Br1B	1623 (3)	4118 (3)	6268 (1)	82 (1)
C1A	3025 (20)	1942 (22)	3579 (7)	41 (5)
C2A	4203 (21)	1842 (23)	3321 (7)	45 (6)
C3A	4041 (22)	886 (25)	2945 (7)	52 (6)
C4A	2764 (22)	190 (24)	2887 (8)	50 (6)
C5A	2542 (20)	−456 (21)	3348 (7)	42 (6)
C6A	2677 (20)	495 (21)	3714 (7)	40 (5)
C7A	2024 (23)	2490 (26)	3193 (8)	59 (7)
C8A	1876 (23)	1471 (25)	2775 (8)	56 (6)
C9A	5065 (23)	663 (26)	2679 (7)	61 (7)
C10A	6197 (25)	1438 (27)	2779 (9)	70 (8)
C11A	6314 (25)	2366 (28)	3139 (9)	70 (7)
C12A	5342 (23)	2590 (25)	3412 (8)	56 (6)
C13A	2466 (24)	57 (27)	4165 (8)	65 (7)
C14A	2120 (25)	−1394 (27)	4211 (8)	65 (7)
C15A	1941 (25)	−2225 (28)	3857 (9)	71 (8)
C16A	2148 (24)	−1868 (27)	3398 (8)	63 (7)
C17A	2230 (20)	4181 (23)	3067 (7)	42 (5)
C18A	522 (30)	924 (34)	2622 (10)	97 (9)
C1B	1492 (20)	1709 (22)	5673 (7)	45 (6)
C2B	1996 (21)	211 (23)	5609 (7)	45 (6)
C3B	3295 (20)	126 (22)	5575 (7)	41 (5)
C4B	3926 (20)	1530 (23)	5650 (7)	45 (6)
C5B	3320 (20)	2583 (22)	5308 (7)	45 (6)
C6B	1990 (20)	2684 (22)	5328 (7)	42 (5)
C7B	2244 (22)	2123 (24)	6161 (8)	55 (6)
C8B	3725 (25)	2071 (27)	6166 (9)	70 (7)
C9B	3867 (21)	−1149 (23)	5513 (7)	48 (6)
C10B	3124 (22)	−2386 (25)	5478 (8)	55 (8)
C11B	1848 (22)	−2317 (25)	5518 (8)	56 (6)
C12B	1249 (21)	−1046 (23)	5575 (7)	49 (6)
C13B	1228 (23)	3550 (25)	5026 (8)	54 (6)
C14B	1843 (25)	4357 (28)	4705 (8)	68 (7)
C15B	3118 (23)	4351 (26)	4695 (8)	59 (6)
C16B	3837 (22)	3472 (24)	4981 (7)	52 (6)
C17B	1772 (24)	1269 (26)	6562 (8)	64 (7)
C18B	4447 (30)	3568 (33)	6265 (10)	90 (9)

[a] Standard deviations are given in parentheses. For the temperature factor the exponent has the form $8\pi^2(\sin\theta/\lambda)^2u$.

dent molecules are given in Table III. The fact that both molecules have the methyl groups in the trans configuration lends powerful support, if such be needed, to the results of the analysis.

Crystal Data on *trans*-7,8-Dibromo-7,8-dimethyldibenzobicyclo[2.2.2]octadiene (11). X-ray crystal structure analysis of this compound was undertaken to determine whether the bromine atoms were in a cis or trans configuration. The crystals were obtained from carbon tetrachloride solution by evaporation. They grew as colorless, transparent needles. The unit cell was found to be monoclinic with dimensions (standard deviations in parentheses) a = 12.003 Å (σ = 0.004 Å); b = 8.043 Å (σ = 0.002 Å); c = 18.023 Å (σ = 0.005 Å); β = 116.84° (σ = 0.02°). The observed density was 1.69 g/cm^3. Assuming four molecules of $C_{18}H_{16}Br_2$ per unit cell gives a calculated density of 1.68 g/cm^3. The cell therefore contains four molecules. The only systematic extinctions observed were in the class ($0k0$) which was absent with k odd. The space group therefore is either $P2_1$ or $P2_1/m$.

Within the limiting sphere of Cu Kα radiation there lie 3550 independent reflections. Measurements were made of the intensities of all reflections for which $2\theta \leq 100°$. Of the 1733 in this category only 1580 with intensities exceeding three times background were used in the analysis. The crystal used in the intensity measurements was 0.3 × 0.3 × 0.5 mm. No absorption correction was applied [μ(Cu Kα) = 72.53 cm^{-1}]. The data were collected using a Syntex P$\bar{1}$ diffractometer in the θ–2θ scan mode, with a scanning rate of 2 deg/min. The Cu Kα line was selected by a graphite crystal monochromator.

Table IV. Approximate Fractional Coordinates of the Bromine Atoms in Two Molecules of *trans*-7,8-Dibromo-7,8-dimethyldibenzobicyclo[2.2.2]octadiene (11)

Atom	x	y	z
Br1	0.5083	0.2292	0.4583
Br2	0.8333	0.4375	0.4333
Br3	0.4700	−0.2292	0.1000
Br4	0.1833	0.0208	0.0458

Location of Bromine Atoms. An unsharpened Patterson synthesis was computed using all 1580 observed intensities. From this synthesis, approximate coordinates were obtained for the four bromine atoms in one half of the unit cell. These are given in Table IV. The bromine atoms which are closest together are Br3 and Br4 and their separation is 4.0 Å. If the bromine atoms were to be in a cis configuration in molecules of this type, the distance between two bromine atoms on the same molecule could hardly exceed 3.4 Å.[34,35] Therefore it was concluded at this point that the bromine atoms were in the trans configuration. Since the trans configuration of the bromine atoms had been established the analysis was not pursued beyond this point.

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Registry No.—**3,** 32363-36-3; **4,** 5445-53-4; **5,** 5445-54-5; **6,** 51229-75-5; **7,** 58240-60-1; **8,** 58267-52-0; **9,** 58240-61-2; **10,** 58240-62-3; **11,** 58267-53-1; **12,** 58240-63-4; **13,** 58311-27-6; **16,** 58310-89-7; **17,** 5472-28-6; **18,** 58240-64-5; **19,** 58267-80-4; **20,** 58240-65-6; **21,** 58240-66-7; **27,** 58240-67-8; **30,** 58240-68-9; anthracene, 120-12-7; *trans*-2-butene, 624-64-6; *cis*-2-butene, 590-18-1; *trans*-7-hydroxymethyl-8-methyldibenzobicyclo[2.2.2]octadiene, 58240-69-0.

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Lanthanide-Induced Chemical Shifts and the Relative Stereochemistry of Multistriatin, 2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane

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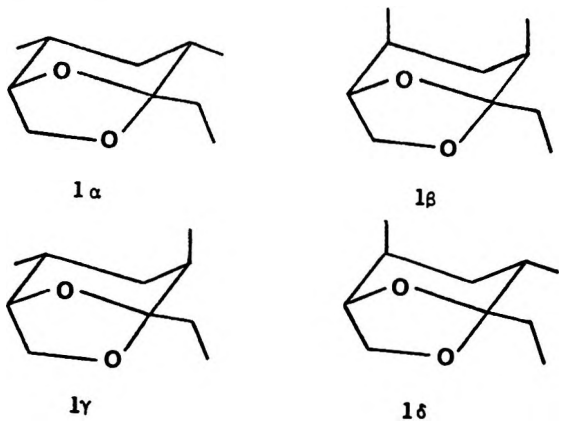
The ^{1}H NMR spectra of the four diastereomers of multistriatin, 2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (1α–δ), and of frontalin, 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (2), were recorded in the presence of the europium paramagnetic shift reagent d_{27}-tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium(III) [(Eu(fod)$_3$]. The binding of Eu(fod)$_3$ to each substrate was investigated by comparing observed shift ratios with those calculated for lanthanide atom positions about each of the oxygen atoms in 1α–δ and in 2. The calculations indicated that for each of these dioxabicyclo[3.2.1]octanes, substrate binding occurred preferentially at one oxygen atom, and that the location of the lanthanide atom was related to steric hindrance about the two potential binding sites. Comparisons of the observed shift ratios for each isomer of 1 with the calculated shift ratios of all isomers of 1 verified the relative stereochemical assignments for these isomers. A correlation between the shift reagent binding site and the biological activity of 1α–δ was observed.

α-Multistriatin (1α), a component of the aggregating pheromone of the European elm bark beetle, *Scolytus multistriatus*, was identified as 2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane by spectrometric and synthetic methods.[2] The previously reported synthesis yielded the four possible diastereomers (1α–δ), and these isomers were separated by GLC and were characterized by NMR, ir, and MS.[3] The spectrometric data in combination with a stereospecific synthesis provided evidence for the assignment of the relative stereochemistry of each of the four diastereomers.



Lanthanide-induced shift (LIS) experiments represented a potential and possibly unique method for testing structural assignments for 1α–δ. The objective of this study was to first evaluate the binding of the shift reagent to 1α–δ and to 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane, frontalin (2), and then to compare any definitive evidence relating the structure of the 6,8-dioxabicyclo[3.2.1]octanes to the previous stereochemical assignments for 1α–δ.

The use of LIS data to test proposed configurations or conformations has been recently reviewed.[4-7] In the case of monofunctional substrates, bonding occurs between donor atom (X) on the substrate (S) and the lanthanide metal atom (L), and a set of equilibria exists for L, S, LS, LS$_2$, and perhaps additional species. This bonding situation is essentially the same for a multifunctional substrate if L binds preferentially to one functional group.

Competitive complexing with multiple donor atoms on the substrate molecule has also been reviewed[8] and is of particular importance in this study of bicyclic ketal structures. Similar donor atoms with identical environments should experience identical L–X bonding, and this expectation has been verified by experiment. However, the lanthanide bonding properties of like functional groups with dissimilar environments can differ. Functional groups usually bond preferentially (OH > ketones $\geq$ esters > ethers); however, this bonding trend can be altered as a consequence of steric hindrance. Such was the case in a computer-assisted LIS study by Farid et al., who described preferential bonding of tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium(III) to an unhindered ether in the presence of a hindered alcohol group.[9] Selective binding in substrates that contain two dissimilar ether groups has also been reported.[8]

The lanthanide-induced change in chemical shift for proton H$_n$ ($\Delta\delta_n$) can be calculated from the pseudocontact term of the McConnell–Robertson equation[10]

$$\Delta\delta_n = K\,(3\cos^2\theta_n - 1)r_n^{-3} \qquad (1)$$

where θ_n is the XLH$_n$ angle and r is the LH$_n$ distance.[5-7] Direct application of this equation to the evaluation of the paramagnetic shifts assumes the absence of a contact contribution to the observed chemical shifts and that the LS complex has effective axial symmetry about the L–X bond. Both

Table I. LIS Data for Frontalin (2)

Shift ratios[a]	Frontalin
$\Delta\delta_1/\Delta\delta_2$	0.45
$\Delta\delta_1/\Delta\delta_3$	0.28
$\Delta\delta_1/\Delta\delta_4$	0.27

[a] [L] = 0.016, [S] = 0.70.

assumptions have been shown to apply, particularly in the case of proton shift studies.[11-13]

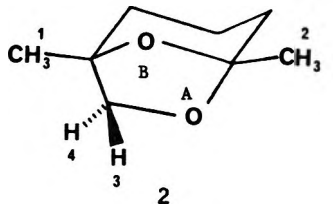
The $\Delta\delta_n$ values can be measured from the δ_n' for a single shifted spectrum and δ_n for an unshifted spectrum ($\Delta\delta_n = \delta_n' - \delta_n$); however, spectra are usually recorded at several [L]/[S] ratios.[7] One $\Delta\delta_i$ value is selected as the reference value, and the remaining $\Delta\delta_n$ are related to $\Delta\delta_i$ as the shift ratio $\Delta\delta_i/\Delta\delta_n$ (calcd) for protons j through n for which observed shift values are available.

$$R = \left[\frac{\Sigma_{n\neq i} w_n\{(\Delta\delta_i/\Delta\delta_n)\text{obsd} - (\Delta\delta_i/\Delta\delta_n)\text{calcd}\}^2}{\Sigma_{n\neq i} w_n(\Delta\delta_i/\Delta\delta_n)\text{obsd}^2}\right]^{1/2} \quad (2)$$

The agreement factor R is used to compare the calculated shift ratios and the corresponding observed shift ratios for several different locations of L. This process is continued, usually as a computer operation, and L is moved through all space surrounding X. A minimum R value is associated with those positions of L which give the best agreement. The calculation is described as being "relatively insensitive (0.2–0.3 Å) to assumed lanthanide position or to error in model coordinates, but sensitive to signal assignments and to substrate stereochemistry".[5]

Results and Discussion

The binding of tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium(III), Eu(fod)$_3$, to the bifunctional dioxabicyclo[3.2.1]octane ring system was initially investigated with a known compound, frontalin (**2**),[14] for



2

which four observable proton signals could be unambiguously assigned. The $\Delta\delta_n$ values for protons 1, 2, 3, and 4 were measured, and the $\Delta\delta_i/\Delta\delta_n$ obsd values are given in Table I.

Two separate Cartesian coordinate systems were calculated (for details see Experimental Section) for the atoms in **2** with OA and OB at the origins in systems A and B, respectively. These coordinate systems, depicting the calculated position of the Eu atom, are diagrammed in Figure 1.

The location of L with respect to substrate atoms H_i–H_n was defined with respect to the donor atom (the origin), as shown by the right-handed coordinate system in Figure 2. The L–O bond was the assumed magnetic axis for the lanthanide–substrate complex, and the length of the L–O bond was $\bar{R}$. The angle Ω is the C_2–O–L bond angle and Φ the dihedral angle between the C_2–C_3 and the L–O bonds.

The lanthanide SHIFT program executed the calculations for a given test structure. The Eu atom was moved by increments through all possible angles of Ω and Φ for reasonable $\bar{R}$ values (2.6–4.0 Å for **2**) for both coordinate systems. The calculation was thus constrained such that the search for minimum R values was limited to a sphere about the donor

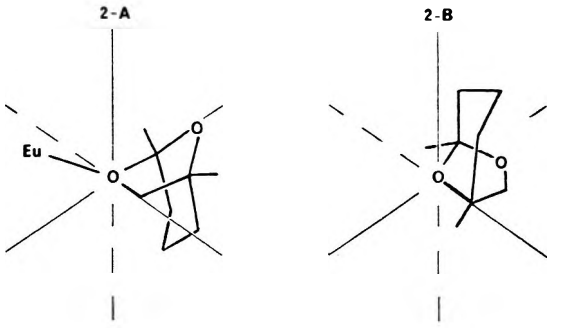


Figure 1. Frontalin (**2**) in coordinate systems A and B depicting the optimum calculated position of the Eu atom.

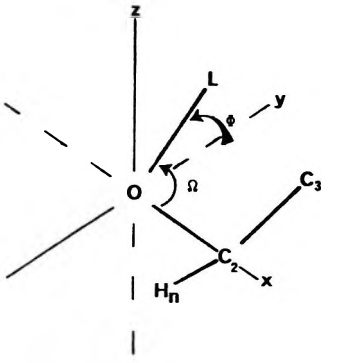


Figure 2. Location of the lanthanide atom with respect to the substrate atoms.

atom with a radius equal to the upper limit of the Eu–O bond length.[5] A set of shift ratios were calculated at each Eu position, and the calculated values were compared to the observed shift ratios. A maximum limit C_x for $\Delta\delta_i/\Delta\delta_n$ calcd − $\Delta\delta_i/\Delta\delta_n$ obsd was set, and if C_x exceeded the limit, the comparison for that Eu position was discarded. When this condition was satisfied, the agreement factor R was calculated.

The R values in combination with the position of the Eu atom relative to the substrate molecule provided a basis for the evaluation of a test structure. Minimum R values were regarded as indicators of relatively good agreement particularly where relatively small values were found for a cluster of Eu positions. The location of the Eu atom was examined, and any positions coincident with other atoms in the substrate were eliminated. The possibility of chance agreement cannot be completely eliminated, particularly when a limited number of proton signals can be observed; however, as our data will demonstrate, these criteria provided a basis for consistent interpretation of the data.

No agreement between calculated and observed shift ratios was obtained for **2** in coordinate system B over the range of R, Ω, and Φ searched, but good agreement (R <0.06) was obtained for coordinate system A with C_x = 0.05. Test calculations indicated that, where good agreement was possible, R values were found for several Eu positions (usually clustered about one point) when C_x was set equal to 0.2. The reduction of C_x to 0.05 yielded the Eu positions with the lowest R values. As shown in Table II, the lanthanide positions which gave low R values are clustered about Ω = 114–120°, Φ = 160°, and $\bar{R}$ = 3.5–3.9 Å.

This result indicated that Eu(fod)$_3$ was bound to OA rather than OB on the exo surface of the five-membered ring, as shown in Figure 1. In this case, preferential bonding was observed in a molecule with endocyclic oxygen atoms. Although the electronic and steric effects related to Eu–O bonding in **2** are difficult to evaluate quantitatively, increased steric hindrance at the OB binding site can be a factor in the preferential bonding of Eu to OA. OA is adjacent to a tertiary and

Table II. Agreement between LIS Data and 6,8-Dioxabicyclo[3.2.1]octane Structures

Test structure and coordinate system	Obsd compd	Ω, deg	Eu location Φ, deg	$\bar{R}$, Å	R
Frontalin (2)					
A	(2)	114–120	160	3.5–3.9	0.06
B	(2)		No agreement[a]		
Multistriatin					
1α-A	1α	72–78	0–20	4.4–4.8	0.09
1α-B	1α	108–112	220	2.0–2.4	0.08
1β-A	1β	114–126	180–240	2.6–4.4	0.05
1β-B	1β	66–72	20	4.4–5.8	0.10
1γ-A	1γ	96–102	200–240	2.8–4.0	0.07
1γ-B	1γ	60–72	20	4.4–4.6	0.10
1δ-A	1δ	108–150	80–120	3.2–4.4	0.05
1δ-B	1δ	78	20	5.8	0.10

[a] For all possible angles of Ω and Φ for $\bar{R}$ values of 2.6–4.0 Å.

Table III. LIS Data for Multistriatin-d_3 Isomers, 1α–δ

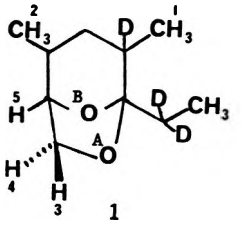
Shift ratios	1α[a]	1β[b]	1γ[c]	1δ[d]
$\Delta\delta_1/\Delta\delta_2$	3.02	1.15	2.48	1.96
$\Delta\delta_1/\Delta\delta_3$	0.45	0.27	0.29	0.41
$\Delta\delta_1/\Delta\delta_4$	0.50	0.24	0.27	0.49
$\Delta\delta_1/\Delta\delta_5$	0.57	0.53	0.50	0.89

[a] [L] = 0.006, [S] = 0.046. [b] [L] = 0.003, [S] = 0.020. [c] [L] = 0.006, [S] = 0.045. [d] [L] = 0.006, [S] = 0.052.

a primary carbon atom while OB is flanked by two tertiary centers, and the approach of the bulky Eu(fod)$_3$ complex to OB should be less favorable than the approach to OA.

This initial experiment demonstrated that selective binding was possible and that good agreement values can be obtained with a monofunctional binding model. Although we would not a priori expect Eu to bind to all 6,8-dioxabicyclo[3.2.1]octanes in the same manner, we were encouraged to apply the LIS calculation to the data obtained from the multistriatin isomers, **1**.

The LIS data were collected for a series of [L]/[S] values for each of the multistriatin isomers, and the data used in the calculation are given in Table III. The $\Delta\delta_i/\Delta\delta_n$ obsd values for a given compound were constant for [L]/[S] values between 0.1 and 0.5, with only minor variability observed for small $\Delta\delta_n$ values (1–3 Hz). The chemical shift assignments and the preparation of 4,11,11-trideuteriomultistriatin (1α-δ-d_3) have been reported.[3] Methyl groups 1 and 2 appeared as two doublets with similar chemical shifts in **1**, but in 1-d_3, methyl



1

group 1 appeared as a singlet. Since methyl groups 1 and 2 could be readily distinguished in the D-labeled isomers, 1α-δ-d_3 were used in the LIS experiments. Since signals for the three protons at C_2 and C_3 were not clearly resolved, they were not used in the LIS calculation. The ethyl group at C_5 probably exhibits an undetermined degree of hindered rotation. Thus, the coordinates for these CH_3 protons could not be assigned with confidence, and this resonance was also excluded from the calculation.

The LIS data obtained for 1α–δ were analyzed in a similar

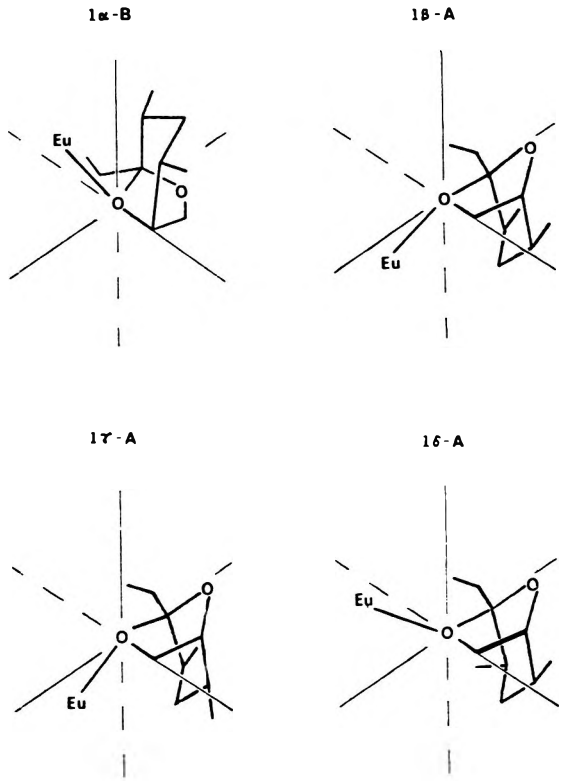


Figure 3. Structures for the Eu(fod)$_3$–multistriatin complexes depicting the optimum position of the Eu atom as determined by the LIS calculation.

manner to that described for compound **2**. As before, both coordinate systems A and B were treated and structures for the Eu(fod)$_3$–multistriatin complexes which gave the best agreement and the most reasonable Eu–O bond length are shown in Figure 3. In the initial calculation, the $\Delta\delta_i/\Delta\delta_n$ obsd values for 1α were compared to the $\Delta\delta_i/\Delta\delta_n$ calcd values for **1α-A** and **1α-B**. In like manner, structures 1β, 1γ, and 1δ in coordinate systems A and B were compared to their respective LIS data. Agreement factor R was printed for $C_x = 0.2$ in all cases except for 1α. In this case, the observed $\Delta\delta_2$ value was very small, thus introducing greater uncertainty in the ratio $\Delta\delta_i/\Delta\delta_2$ obsd, and it was necessary to increase the value of C_1 ($\Delta\delta_1/\Delta\delta_2$ obsd − $\Delta\delta_1/\Delta\delta_2$ calcd) to 1.5. Angles Ω and Φ were varied over all space for $\bar{R}$ values from 2.0 to 5.8 Å. Good agreement could be obtained between the $\Delta\delta_i/\Delta\delta_n$ obsd values for 1α–δ and the corresponding $\Delta\delta_i/\Delta\delta_n$ calcd values for the assigned structures (Table II). Similar agreement factors were obtained with both coordinate systems A and B; however, the

Table IV. Comparisons of 1α–δ LIS Data with Structures 1α–δ[a,b]

Structure, coordinate system	Source of LIS data: 1α	1β	1γ	1δ
1α-B	+	0	0	0
1β-A	0	+	0	0
1γ-A	0	0	+	0
1δ-A	0	+	0	+

[a] + = agreement; 0 = no agreement. [b] Lanthanide positions were varied over all values of Ω and Φ and $\bar{R}$ values from 2.6 to 4.6 Å. Agreements were based on minimum R values for reasonable structures of the Eu(fod)$_3$–substrate complex.

location of the Eu atom and the R values suggested that Eu(fod)$_3$ bonded preferentially to one of the oxygen atoms (vide infra).

In the case of **1α**, a consideration of the $\bar{R}$, θ, and Φ values for those Eu positions which gave the best agreement between observed and calculated shift ratios indicated that Eu was coordinated to OB. As shown in Figure 3 and Table II, the Eu positions which gave minimum R values were clustered about one point which was over the exo surface of the six-membered ring. The location of the Eu atom was supported by the calculation for coordinate system A, since low R values were obtained for Eu positions coinciding with those obtained for the B system. The Eu–OA bond is nearly collinear with the assumed magnetic axis defined by the Eu–OB bond. Thus, the θ_n and r_n values (eq 1) in coordinate systems A and B were nearly equal, and these values would give rise to similar calculated shift ratios. In view of the equivalent location of the Eu atom with respect to donor atoms OA and OB, the "more reasonable" $\bar{R}$, θ, and Φ values associated with system B suggested that the coordination of Eu(fod)$_3$ to **1α** occurred primarily to OB.

The results obtained for **1β** and **1γ** provided an interesting reversal of the **1α** bonding situation. Consideration of R values and the Eu–O bond distance ($\bar{R}$) indicated that Eu(fod)$_3$ bonded preferentially to OA in both **1β** and **1γ** (Table II) with the Eu atom located on the endo surface of the five-membered ring (Figure 3). As in the **1α** case, the Eu–OA and the Eu–OB bonds were nearly collinear, and low R values were obtained in both coordinate systems with the Eu position in B corresponding exactly to those in A. Calculations for the **1δ** isomer gave low R values for a cluster of Eu positions on the exo surface of the five-membered ring in system A, as shown in Table II and Figure 3. For this isomer, however, the Eu–OA and Eu–OB bonds did not coincide and relatively poor agreement and unreasonable $\bar{R}$ values were found in system B. The single Eu position for B was on the exo surface of the five-membered ring, with a relatively long (5.8 Å) Eu–OB bond length. These results suggested that in **1δ**, like **1β** and **1γ**, OA was the primary bonding site for the Eu atom.

In a second series of calculations the agreement between the calculated shift ratios for structures **1α–δ** and the "wrong" LIS data was tested. The best agreement for the **1α** data and the **1α** structure was obtained with a coordinate system B. Consequently, the calculated shift ratios for **1α-B** were compared to the LIS data for **1β**, **1γ**, and **1δ**, and, as shown in Table IV, no reasonable agreement values were obtained. For **1β**, **1γ**, and **1δ**, coordinate systems A gave the best agreement with the **1β**, **1γ**, and **1δ** LIS data, respectively. Calculated shift ratios for **1β-A** were therefore compared to the observed shift ratios for **1α**, **1γ**, and **1δ**, and likewise structures **1γ-A** and **1δ-A** were compared to the observed shift ratios for **1α**, **1β**, and **1δ**, and for **1α**, **1β**, and **1γ**, respectively. The comparisons of the calculated **1δ-A** shift ratios and the observed **1β** values gave low R values for Ω = 114–156°, Φ = 140–200°, and $\bar{R}$ = 2.6–4.4 Å. However, equally good agreement values were obtained for comparison of the observed and calculated shift ratios for **1β** and for **1δ** and agreement was not found for the comparison of the calculated **1β-A** shift ratios and the observed **1δ** data. Furthermore, low R values for a cluster of reasonable Eu positions were not found for any of the remaining wrong data comparisons. Thus we conclude that the low R values for the **1δ-A** vs. **1β** (observed data) comparison represented a coincidental agreement which is not unexpected in view of the statistical nature of the calculation.

The structures assigned to **1α–δ** based on the LIS data are in accord with those determined by other means,[3] and in each isomer the location of the Eu atom was consistent with the relative stereochemistry of the structure. Only in **1α** are methyl groups 1 and 2 both endo and this configuration leaves the exo surface of the six-membered ring relatively unhindered. This unique situation was reflected in the binding of Eu to OB. In the three remaining isomers, at least one methyl group was exo, thus hindering the approach of Eu(fod)$_3$ to OB. This steric hindrance was apparently sufficient to make OA the preferred binding site for Eu(fod)$_3$ in **1β**, **1γ**, and **1δ**. In **1β** and **1γ**, methyl group 1 was exo and the calculated position of the Eu atom was on the endo surface of the five-membered ring. This situation was altered in **1δ** where methyl group 1 was endo, and Eu(fod)$_3$ occupied a position on the exo surface of the five-membered ring. This result further indicated that stereochemical features of the substrate were reflected in the calculated position of the Eu atom.

Conclusions

We have successfully utilized LIS data to verify the structures of a series of diastereomeric 6,8-dioxabicyclo[3.2.1]octanes. The calculation was selective in relating each set of experimental data with a single structure. The calculated location of the Eu atom was in each case consistent with the structural features of the compound and indicated that Eu–substrate bonding occurred primarily at one site. These results reflected the importance of steric factors in the bonding of Eu(fod)$_3$ to these bifunctional substrate molecules.

An additional feature of this study was the correlation that was observed between the calculated Eu bonding site and the biological activity of **1α–δ**. Isomers **1α–δ** had been tested as one component of the aggregating pheromone for *S. multistriatus*, and naturally occurring **1α** was the only isomer that exhibited biological activity.[15] Molecular geometry and electrostatic effects of odorant molecules are important factors in determining olfactory responses, and current theories of olfaction have related the unique olfactory response elicited by an odorant to the fit of the odorant molecules on receptor sites.[16–18] Our finding that the fit of **1α** on the Eu(fod)$_3$ complex differed from that of **1β**, **1γ**, and **1δ** paralleled the observation that **1α** exhibited unique biological activity. This single comparison of Eu(fod)$_3$ bonding and olfactory responses does not prove a relationship; however, these results indicate that Eu(fod)$_3$ could be mimicking some steric and/or electronic features of the olfactory receptor site.

Experimental Section

Lanthanide Shift Experiments. The NMR spectra were recorded for **1α–δ** in carbon tetrachloride solution in the presence of freshly sublimed d_{27}-tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium (III), Eu(fod)$_3$. The carbon tetrachloride was dried over 4 Å molecular sieves, and all transfers were performed in an inert atmosphere. Samples containing 0.1–1 mg of substrate in 50 μl of solvent were filtered into the inner cell of a coaxial cell (Wilmad, 520-2), and benzene-d_6 (100% D)–Me_4Si solution was placed in the outer cell. Spectra for **2** were recorded in $CDCl_3$ solution. All spectra were recorded in the Fourier transform mode with a Varian XL-100

NMR spectrometer. Spectra were recorded at four [L]/[S] values for each substrate compound, and δ_n values were obtained from the spectra. The $\Delta\delta_i/\Delta\delta_n$ obsd values were constant within the experimental accuracy of the measurements. The values for **2** and for **1α–δ**, which were used in the calculations, are given in Tables I and III, respectively.

Calculations. The coordinates for each atom in each of the substrate structures were calculated with the COORD program.[7] Two coordinate systems were calculated for each molecule. The origins for systems A and B were OA and OB, respectively. The agreement between the observed shift ratios for a given substrate were calculated with the SHIFT program.[7]

Preparation of 4,11,11-Trideuteriomultistriatin Isomers (1α–δ). A sample of multistriatin (1) was refluxed in 1 M D_3PO_4–tetrahydrofuran solution and worked up according to the previously described method.[3]

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Registry No.—**1α**, 54815-06-4; **1β**, 54832-20-1; **1γ**, 54832-21-2; **1δ**, 54832-22-3; **2**, 28401-39-0.

References and Notes

(1) (a) Lederle Laboratories, Pearl River, N.Y. 10965. (b) This work was supported in part by the U.S. Forest Service, the Elm Research Institute, the Rockefeller Foundation, and the College of Environmental Science and Forestry. (c) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.
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Synthesis of Samandarine-Type Alkaloids and Analogues[1,2]

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Facile stereoselective syntheses of samandarine and its regioisomers are described.

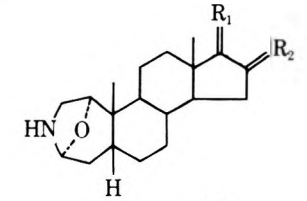
European salamanders, *Salamandra maculosa taeniata* and *S. maculosa maculosa*, are known to secrete alkaloidal venoms from the glands located on the skin, probably for defensive purposes. The chemical structures of these alkaloids had been vigorously investigated by Schöpf and Habermehl's group over a number of years, and the structure of the major alkaloid, samandarine (**1**), was first established by X-ray crystallography in 1961.[3]

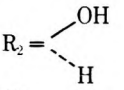
A group of alkaloids represented by samandarine are characterized by the presence of a peculiar 6-aza-8-oxabicyclo[3.2.1]octane ring system in the A ring of steroidal nuclei.

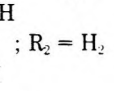
Owing to this peculiar bridged system and the reported neurotoxicity of these naturally scarce substances, the synthesis of samandarine and its analogues has been pursued by several groups. A multistep synthesis of samandarine was first reported by a Japanese group.[4] A few other attempts to synthesize samandarine and the ring system have also been reported.[5]

Since there are several established ways to introduce an oxygen function at C-16, the major problem inherent in the synthesis of these alkaloids is in the construction of the bridged oxazolidine system with the correct stereochemistry.

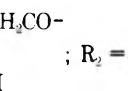
In this paper, the author reports a general procedure for the preparation of the bridged oxazolidines from α,β-unsaturated cyclic ketones and a facile, stereoselective formal synthesis of samandarine (**1**).



1, $R_1 = H_2$; $R_2 =$ 

21, $R_1 =$  ; $R_2 = H_2$

22, $R_1 = H_2$; $R_2 = O$

23, $R_1 =$  ; $R_2 =$ 

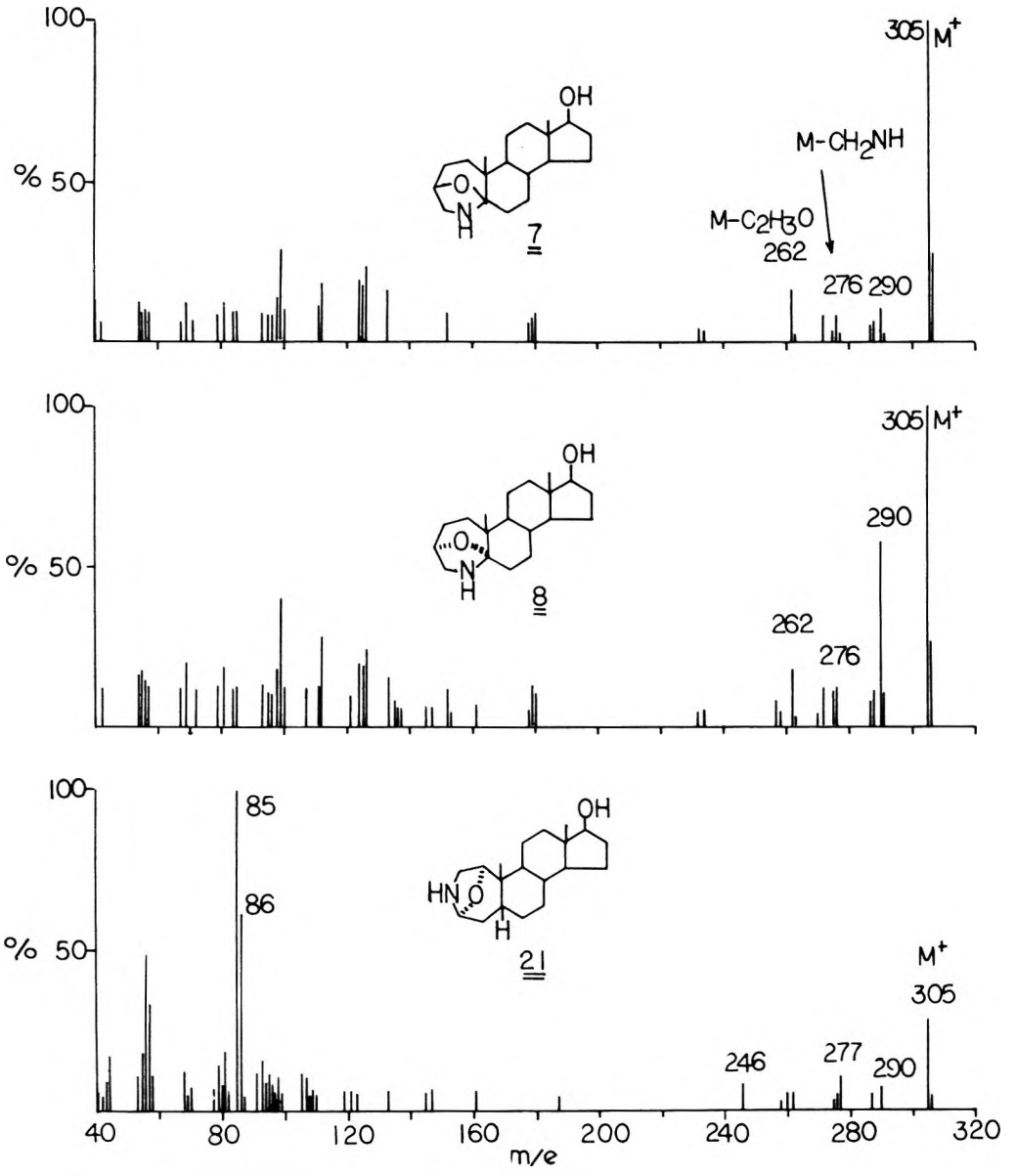
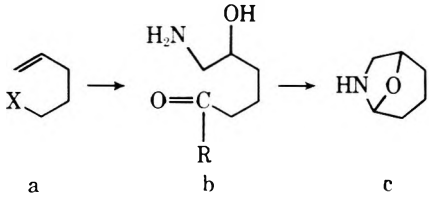


Figure 1. EI mass spectra of samandarin regioisomers, **7**, **8**, and **21** (70 eV, 220 °C).

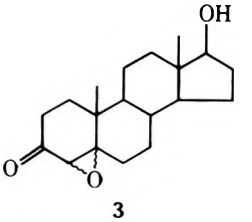
The 6-aza-8-oxabicyclo[3.2.1]octane ring system is essentially the hemiaminoacetal (ketal) of the amino alcohol (b) formed by an intramolecular condensation. Therefore, it seemed to be an easy approach to synthesize a δ,ϵ-unsaturated compound of type a and to functionalize the double bond and the group X in an appropriate manner to effect subsequent cyclization (Scheme I). In order to test this approach, the

Scheme I



synthesis of 3,5-epoxy-4a-aza-*A*-homoandrostan-17β-ol, a regioisomer of samandarine, was first attempted.

A mixture of testosterone α- and β-exoxides (**3**), which can be obtained in a high yield by H_2O_2–NaOH treatment of testosterone (**2**), was allowed to react with *p*-toluenesulfonylhydrazine in a mixture of methylene chloride and acetic acid.[6] The acetylene derivative (**4**) was obtained in a 70% overall yield from testosterone. Partial hydrogenation of the



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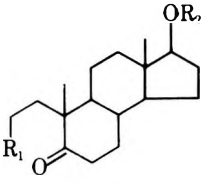

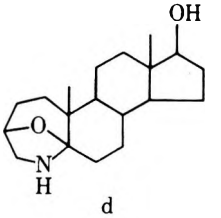

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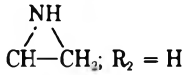
7, **8**

4. R_1 = C≡CH; R_2 = H

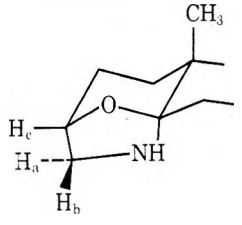
5. R_1 = CH=CH_2; R_2 = Ac

6. R_1 =  ; R_2 = H

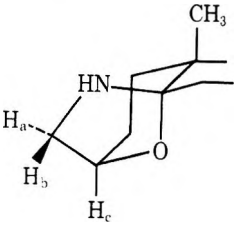
acetylene group of 4 with Lindler catalyst and subsequent acetylation gave the seco olefin (5) in a ca. 80% yield. Reaction of 5 with *N,N*-dichlorourethane followed by bisulfite and alkali treatment[7] gave a stereoisomeric mixture of the aziridine derivative (6) (ν_{NH} 3300 cm^{-1}). When the isomeric mixture (6) was heated in 2 NH_2SO_4 on a steam bath for 2 h, it afforded two isomeric chloroform-soluble products, 7, mp 70–73 °C (hydrate), and 8, mp 221–222 °C, with identical compositions of $C_{16}H_{33}NO_2$. Both 7 and 8 show typical absorptions for oxazolicines (1050–800 cm^{-1}), no carbonyl absorption in the ir spectra, and almost identical ^1H NMR and mass spectra (Figure 1) except for the difference in the chemical shifts of the 19-methyl groups. The ABX system seen around δ 3.0 is fully compatible with the structure d. The alternative structure in which the nitrogen and oxygen atom are interchanged was ruled out because the chemical shifts indicate that the methylene group is linked to the nitrogen atom. It was fully expected that the aziridine opens in the non-Markownikoff manner. The combined yield of 7 and 8 was ca. 40%. The rest of the products were very polar, and were not extracted with chloroform. This fraction probably consisted of the isomeric carbinolamines, which apparently do not cyclize under the employed condition.[8]

The structures A and B are tentatively assigned to 7 and 8 respectively, for the following reasons. The lower chemical shift of the 19-methyl group of 8 may be explained by the anisotropic effect of the β-oriented nitrogen group in the structure B. The compound 8 has a bigger coupling constant, J_{H_b,H_c}, than the isomer 7 in accordance with the implication of the model examination (Table I), although this argument may not be so reliable owing to the uncertain influence of the heteroatoms.

Table I. Expected and Observed ^1H NMR Data for 7 and 8



A



B

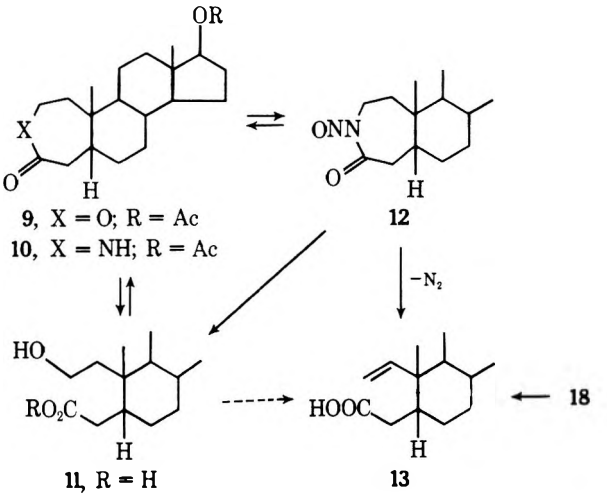
	Dihedral angles obtained from the models	Expected J, Hz	Observed J, Hz	19-CH_3, ppm
Structure A	H_b, H_c = 35°	6.5 7	6.0	
	H_a, H_c = 85°	0	0	0.90
Structure B	H_b, H_c = 25°	8.0 8	7.0	
	H_a, H_c = 95°	0	0	1.07

For the synthesis of samandarine itself, the same procedure used for the synthesis of 7 and 8 could be applied. However, the preparation of the desired starting compounds, Δ^2-1-ones in the A/B cis steroids, is lengthy if not unattainable. Consequently, alternative routes to the Δ^1-2,3-seco compound with an appropriate function at C-3 were investigated.

Attempts to convert easily obtainable 2,3-seco steroids,[9] lactone 9 or lactam 10, to the desired Δ^1-2,3-seco compound proved to be futile. Dehydration of the seco hydroxy acid 11 and its esters, which can be obtained easily by Baeyer–Villiger oxidation of 17β-hydroxy-5β-androst-3-one, by various methods failed owing to their easy conversion to the seven-membered lactone 9.

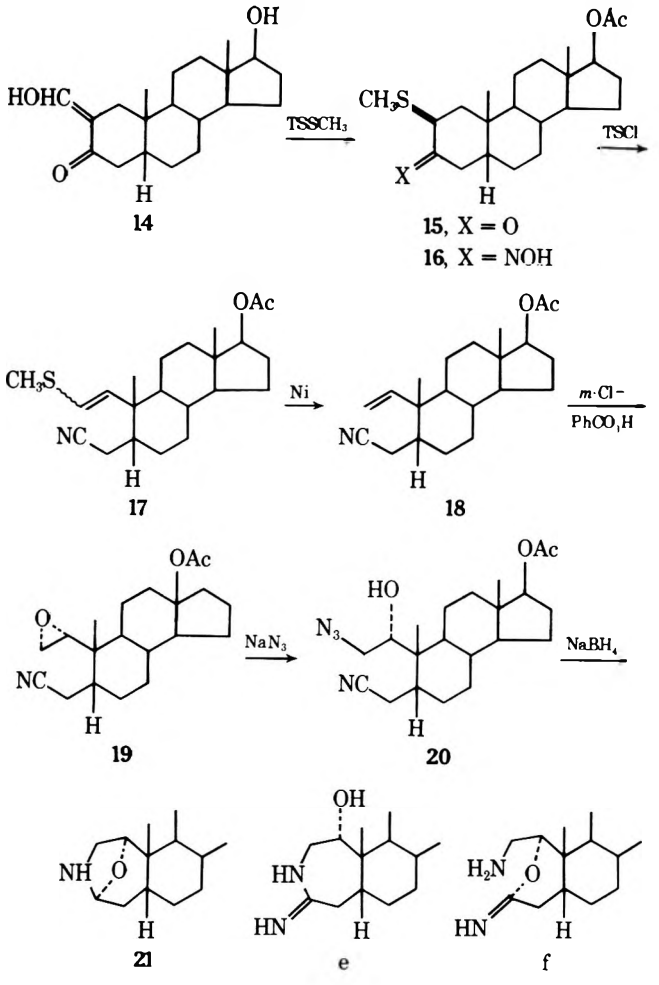
Huisgen reported that under selected conditions, the decomposition of *N*-nitroso lactams yields ω-unsaturated acids in addition to the corresponding lactones or hydroxy acids.[10] The stable *N*-nitroso compound 12, which was prepared by the treatment of the lactam 10[11] with sodium nitrite in acetic acid, was subjected to decomposition under various conditions (Scheme II). The major reaction product was always the lactone 9, or the hydroxy acid 11 if the reaction was carried out under a basic condition. When the decomposition was done in dimethyl sulfoxide, less than a 5% yield of the desired methylene acid (13) was obtained. Meanwhile, successful ring cleavage to construct the 2,3-seco-5β-androstane skeleton of samandarine was accomplished by the procedure which Autrey and Scullard had used for the synthesis of corynantheine.[12] The hydroxymethylene derivative (14)[13] was treated with 1.3 mol of methyl *p*-toluenethiosulfate in the presence of potassium acetate in boiling ethanol.[14] The product isolated after acetylation, in 80% yield, was 17β-acetoxy-2β-methylthioandrostan-3-one (15) (Scheme III). The equatorial 2β configuration was expected for the introduced methylmercapto group, and it was confirmed by the appearance of the axial C-2 hydrogen signal in the ^1H NMR spectrum, δ 3,46 (q, J = 6, 13 Hz). The reaction of 15 with hydroxylamine chloride in pyridine afforded the oxime 16, in a quantitative yield. The treatment of 16 with *p*-toluenesulfonyl chloride in refluxing pyridine for 30 min gave a seco nitrile product, 17, in 65% yield as the sole product.[15] It is known that steroidal 3-ketones afford about 1:1 mixtures of the syn and anti oximes, which upon Beckmann rearrangement give the corresponding isomeric lactams, respectively. It seemed improbable that the presence of the 2β-methylmercapto group occasions the exclusive formation of one isomer, and indeed, the TLC examination showed the presence of two oximes. The apparent loss of directional influence in the Beckmann rearrangement (fragmentation) may be explained either by the equilibration of the oximes under the conditions employed or by a highly favored fragmentation due to the electron-donating methylmercapto group.[16] Removal of the methylmercapto group in 17 without affecting the double bond or nitrile group was accomplished by treatment with Levin's deactivated Raney Ni.[17] The methylene nitrile (18) was obtained in 40–65% yields. The poor yields resulted from the formation of the corresponding saturated nitrile derivative which seemed unavoidable even under highly controlled conditions.

Scheme II



Treatment of 18 with *m*-chloroperbenzoic acid gave preferentially one epoxide, 19. In prior model examination, the desired 1*R* epoxide was expected to be the major product,[18] and this assumption was supported by subsequent successful conversion of 19 to the final product. The non-Markownikoff opening of the epoxide with NaN_3 in refluxing methylcello-

Scheme III



solve gave the azide **20** in a quantitative yield. The conversion of **20** to the final product, oxazolidine **21**, which involves the partial reduction of the nitrile to the aldehyde level, reduction of the azide group to the amine, and hydrolysis of the 17-acetyl moiety, was accomplished in one step by reduction with $NaBH_4$ in refluxing 2-propanol.[19] Extraction of the reaction mixture with chloroform gave almost pure crystals of **21** in about 60% yield. Recrystallization from acetone gave a specimen, mp 191–193 °C, ir 852 and 834 cm^{-1} (oxazolidine), which was identified with the authentic sample[4] by mixture melting point, ir, and TLC. The mass spectrum of **21** was practically identical with that of samandarine[20] (Figure 1). Although a nitrile group is not a normal target of $NaBH_4$ reduction, the outcome of the reaction was not entirely unexpected. Under the basic condition in the reduction, the nitrile group formed either cyclic amidine (e) or imino ester (f) which is subject to $NaBH_4$ reduction, and concomitant cyclization to the rigid oxazolidine ring prevented further reduction.[21]

Since **21** had already been converted to samandarine (**1**), which was further modified to samandarone (**22**) and a samandaridine (**23**), this work formally represents a new stereoselective synthesis of these alkaloids.

Experimental Section

All melting points were measured on a Kofler block and are uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 458 in specified phases. Mass spectra were taken with a CEC Model 104. NMR spectra were measured with a JEOL HR 60 model.

17β-Acetoxy-4,5-secoandrost-3-en-5-one (5) 17β-Hydroxy-4,5-secoandrost-3-yn-5-one (**4**,[6] 160 mg) was dissolved in benzene (10 ml) and shaken under H_2 in the presence of Lindler catalyst (25 mg) and 1 drop of quinoline. After the uptake of 1 mol of H_2, the catalyst was filtered off and the solution was washed with dilute HCl, dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in a mixture of pyridine and acetic anhydride (2:1) and was left at room temperature for 12 h. The mixture was poured onto ice and extracted with ether. The ethereal extract was washed with dilute HCl, $NaHCO_3$ solution, and water, and dried over Na_2SO_4. Evaporation of the ether gave a crystalline residue which was crystallized from petroleum ether to prisms (**5**): mp 73–75 °C; ir (Nujol) 1740 (CH_3CO), 1700 (C=O), 1638 and 910 cm^{-1} (C=CH_2); yield 136 mg.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.68; H, 9.70. Found: C, 76.04; H, 9.64.

17β-Hydroxy-3,4-imino-4,5-secoandrostan-5-one (6). To a solution of 17β-acetoxy-4,5-secoandrost-3-en-5-one (**5**, 1.03 g) in dry benzene (10 ml) was added *N,N*-dichlorourethane (0.49 g) and the solution was refluxed for 2 h. After cooling, the mixture was diluted with ether and washed with 5% $NaHSO_3$ solution. After evaporation of the solvent, the residue (1.1 g) was redissolved in a 5% alcoholic KOH solution and heated on a steam bath for 1 h. The reaction mixture was diluted with ether and extracted with 2% HCl solution. Basification of the HCl extract with a 5% NaOH solution liberated an oily substance which was extracted with chloroform. Evaporation of the chloroform layer afforded a colorless, resinous residue **6** (80 mg), *m/e* 305 (M^+), ir (neat) 3500 (OH), 3300 cm^{-1} (NH).

3,5-Epoxy-4-aza-*A*-homoandrostan-17-ol (7) and 8. 17β-Hydroxy-3,4-imino-4,5-secoandrostan-5-one (**6**, 400 mg) was dissolved in 2 N H_2SO_4 (10 ml) and heated at 80 °C for 2 h. The cooled solution was basified with a 5% NaOH solution and extracted with chloroform (50 ml × 3). Evaporation of the chloroform extract left a residue (85 mg), only two spots on TLC (silica gel, 5% MeOH in $CHCl_3$), which was chromatographed on a silica gel column. Elution with 5% methanol–chloroform afforded two pure compounds, **7** and **8** in the order of elution. **7**: crystals from methanol–water; mp 70–73 °C (hydrated crystals); ir (Nujol) 3450, 3300, 1047, 1018, and 895 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.74 (3 H, s, 18-CH_3), 0.90 (3 H, s, 19-CH_3), 2.79 (1 H, d, J = 10 Hz), 3.16 (1 H, q, J = 6, 10 Hz), 3.64 (1 H, t, 17-H), and 4.42 ppm (1 H, m); mass spectrum (Figure 1).

Anal. Calcd for $C_{19}H_{31}NO_2 \cdot H_2O$: C, 70.55; H, 10.28; N, 4.33. Found C, 70.55; H, 10.70; N, 4.37.

8: from $CHCl_3$; mp 221–222 °C; ir (Nujol) 3460, 3310, 1020, 1005, 900, and 878 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.74 (3 H, s, 18-CH_3), 1.07 (3 H, s, 19-CH_3), 2.75 (1 H, d, J = 10 Hz), 3.14 (1 H, q, J = 7, 10 Hz), 3.61 (1 H, t), and 4.44 ppm (1 H, m); mass spectrum (Figure 1).

Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.65; H, 10.06; N, 4.34.

17β-Acetoxy-*N*-nitroso-3-aza-*A*-homo-5β-androstan-4-one (12). 17β-Acetoxy-3-aza-*A*-homo-5β-androst-4-one (**11**, 1 g) was dissolved in an 1:1 mixture of acetic anhydride and acetic acid (50 ml), and $NaNO_2$ (300 mg) was added to the mixture under stirring at 0 °C. After stirring for 2 h, the mixture was poured onto ice, and the yellow, crystalline precipitate was collected by filtration and washed with water. Recrystallization from CH_2Cl_2–2-propanol gave a yellow prism: mp 146–148 °C; ir (Nujol) 1745 (acetate), 1710 (C=O), 1540 cm^{-1} (NO); yield 920 mg.

Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 67.71; H, 8.66; N, 15.04. Found: C, 67.54; H, 8.55; N, 15.00.

17β-Hydroxy-2,3-seco-5β-androst-1-en-3-oic Acid (13). The nitrosolactam **12** (500 mg) was dissolved in dimethyl sulfoxide (50 ml) and heated at 80 °C for 2 h. Evolution of nitrogen was observed during this period. The reaction mixture was diluted with ether and washed thoroughly with water, and then extracted with 5% $NaHCO_3$ solution. After acidification with dilute HCl, the acidic compound was extracted with ethyl acetate. Evaporation of the solvent left an acidic fraction (21 mg), which was saponified with 5% NaOH solution. After usual workup, the hydroxycarboxylic acid, **13**, was obtained and recrystallized from ethyl acetate, mp 183–186 °C, ir (Nujol) 3400 (OH), 1700 (-COOH), and 910 cm^{-1} (C=CH_2), which was identical with a specimen obtained by hydrolysis of **18**.

17β-Acetoxy-2β-methylthio-5β-androstan-3-one (15). To a boiling solution of 17β-hydroxy-2-hydroxymethylene-5β-androst-3-one (**14**, 1.0 g) in 10 ml of ethanol containing KOAc (1.0 g) was added a solution of methyl *p*-toluenethiosulfate (635 mg) in ethanol (10 ml). The solution was heated for an additional 10 min. After addition of water, the mixture was reduced in volume under vacuum and extracted with ether. The ethereal solution was washed with dilute NaOH solution and water, dried, and evaporated to dryness. The glassy residue was then acetylated by the usual method. Recrystallization of the acetate from methanol gave prisms of **15**: mp 190–192 °C; ir (KBr) 1735, 1248 (acetate), 1690 cm^{-1} (3CO); ^1H NMR ($CDCl_3$) δ 0.82 (3 H, s) 1.04 (3 H, s), 2.04 (3 H, s) 2.10 (3 H, s), 3.46 (1 H, q, J = 6, 12 Hz), 4.60 ppm (1 H, m).

Anal. Calcd for $C_{22}H_{34}O_3S$: C, 69.79; H, 9.05; S, 8.39. Found: C, 70.07; H, 9.12; S, 8.63.

17β-Acetoxy-2β-methylthio-5β-androstane-3-ketoxime (16). 17β-Hydroxy-2β-methylthio-5β-androstan-3-one (**15**, 150 mg) was heated with hydroxylamine hydrochloride (200 mg) in pyridine on a steam bath for 1 h. After addition of water to the mixture, precipitated crystals were collected and recrystallized from methanol–water to prisms, **16**: mp180–183 °C; ir (KBr) 3270 (NO–H), 1730 (acetate), 1660 cm^{-1} (C≡N); yield 137 mg.

Anal. Calcd for $C_{22}H_{35}O_3NS$: C, 67.13; H, 8.96; N, 3.56; S, 8.14. Found: C, 67.05; H, 8.98, N, 3.42; S, 8.34.

17β-Acetoxy-2-methylthio-2,3-seco-5β-androst-1-ene-3-nitrile (17). The oxime **16** (300 mg) was dissolved in pyridine (6 ml) containing *p*-toluenesulfonyl chloride (450 mg). The solution was refluxed for 30 min under N_2. The resulting reaction mixture was diluted with ether and washed with water. Evaporation afforded a residue (280 mg) which was chromatographed on silica gel (17 g). Elution with CH_2Cl_2 gave crystals (185 mg), which were recrystallized from methanol, **17**: mp 105–107 °C; ir (Nujol) 2250 (C≡N), 1730 (acetate), 1570 cm^{-1} (–SC=C).

Anal. Calcd for $C_{22}H_{33}NO_2S$: C, 70.36; H, 8.86; N, 3.73; S, 8.54. Found: C, 70.44; H, 8.95; N, 3.41; S, 8.71.

17β-Acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (18). The thioenol ether **17** (130 mg) was heated with deactivated Raney Ni[17] (1.3 ml) in methanol (30 ml) under reflux for 1.5 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness. Crystallization from isopropyl ether gave needles: mp 147–148 °C; ir (Nujol) 2250 (C≡N), 1740 (acetate), 1640, 924 cm^{-1} (C=CH_2).

Anal. Calcd for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found: C, 74.54; H, 9.30; N, 4.12.

(1*R*)-1,2-Epoxy-17β-acetoxy-2,3-seco-5β-androstane-3-nitrile (19). The seco olefin **17** (100 mg) was dissolved in $CHCl_3$ (5 ml) containing *m*-chloroperbenzoic acid (200 mg, 70% pure) and was left at room temperature for 48 h. The reaction mixture was diluted with sodium sulfite solution, $NaHCO_3$, and water. Evaporation of ether gave a crystalline residue, which was recrystallized from methanol and H_2O to needles: mp 134–135 °C; ir (Nujol) 2250 (C≡N), 1750 (acetate), 1060, and 1030 cm^{-1}; yield 81 mg.

Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.02; H, 9.21; N, 3.85.

17β-Acetoxy-2-azido-1-hydroxy-2,3-seco-5β-androstane-3-nitrile (20). The epoxide **19** (100 mg) was dissolved in methyl Cellosolve (5 ml) containing H_2O (0.3 ml), NaN_3 (150 mg), and NH_4Cl (8.5 mg). The mixture was heated under reflux for 1.5 h. Dilution of the mixture with H_2O separated crystals (101 mg), which were recrystallized from ether–isopropyl ether to prisms (**20**): mp 191 °C (sinters at 178 °C); ir (Nujol) 3480 (OH), 2770 (C≡N), 2110 (–N_3), and 1735 cm^{-1} (acetate).

Anal. Calcd for $C_{21}H_{32}N_4O_3$: C, 65.26; H, 7.82; N, 14.50. Found: C, 65.46; H, 7.90; N, 14.49.

1,4-Epoxy-3-azahomo-5β-androstan-17β-ol (21). To a solution of the azide **20** (20 mg) in 2-propanol (1 ml) was added $NaBH_4$ (10 mg) and the mixture was heated at 90 °C under N_2 for 16 h. After evaporation of the solvent, the residue was dissolved in 5 ml of water and extracted with $CHCl_3$ several times. Evaporation of the extract gave a crystalline mass which showed only one spot on TLC (silica gel, 15% MeOH–H_2O). Recrystallization from methanol gave prisms [mp 191–193 °C; ir (KBr) 3420 (OH), 3320 (NH), 1115, 1060, 1015, 852, 834 cm^{-1}; ^1H NMR δ $CDCl_3$) 0.76 (3 H, s), 0.86 (3, H, s), 3.00 (3 H, m), 3.66 (1 H, t), and 4.19 ppm (1 H, q)], which was identified with an authentic sample sent by Dr. Oka by mixture melting point, TLC, ir, and mass spectra (Figure 1).

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Registry No.—**1**, 467-51-6; **4**, 17541-44-5; **5**, 58673-15-7; **6**, 58673-16-8; **7**, 58673-17-9; **8**, 58673-18-0; **11**, 21522-17-8; **12**, 58673-19-1; **13**, 58673-20-4; **14**, 52129-23-4; **15**, 58673-21-5; **16**, 38623-74-4; **17**, 38623-75-5; **18**, 38623-76-6; **19**, 38623-77-7; **20**, 38623-78-8; **21**, 25484-32-6.

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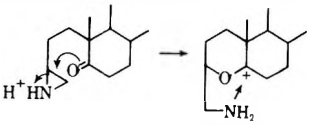

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Clemmensen Reduction of 2-Acetylfluorene. Pathways for the Formation of 2,3-Di(2-fluorenyl)butane and Its Homologues

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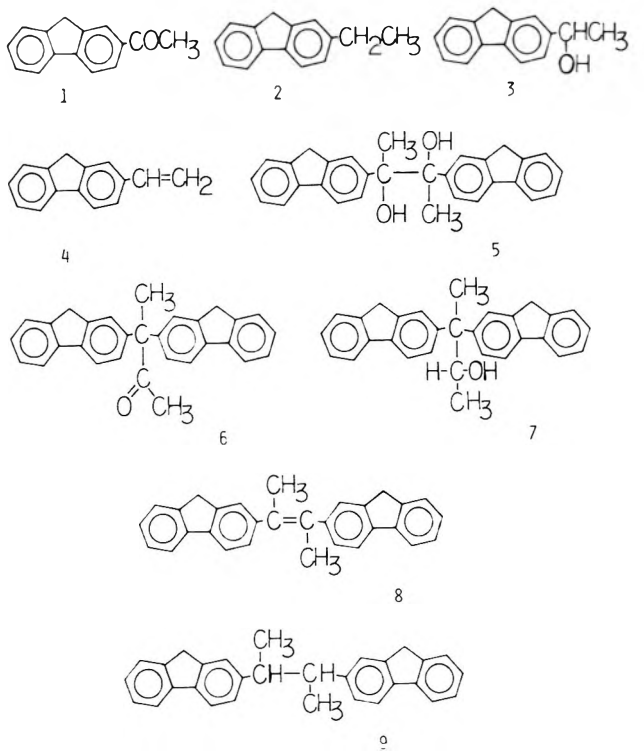
The Clemmensen reduction of 2-acetylfluorene gave not only 2-ethylfluorene but also 2-(α-hydroxyethyl)fluorene, 2-vinylfluorene, *cis*- and *trans*-2,3-di(2-fluorenyl)-2-butene, *meso*- and *dl*-2,3-di(2-fluorenyl)butane, 2,3-di(2-fluorenyl)-2,3-butanediol, 3,3-di(2-fluorenyl)-2-butanone, and 3,3-di(2-fluorenyl)-2-butanol. The confirmation of these compounds was achieved by established syntheses. The Clemmensen reduction of 2-acetylfluorene may proceed through the corresponding carbinol, 2-(α-hydroxyethyl)fluorene, to the normal reduction product, 2-ethylfluorene.

The Clemmensen reduction of 2-acetylfluorene (**1**)[1,2] has been reported by Campbell and Wang[3] to yield only 2-ethylfluorene (**2**)[4-6] in 45% yield.

The present paper deals with the reinvestigation of this reduction and **1** was found to form not only **2** (76%) but also intermediary compounds, 2-(α-hydroxyethyl)fluorene (**3**)[7] and 2-vinylfluorene (**4**),[6-8] and the related dimeric products, namely 2,3-di(2-fluorenyl)-2,3-butanediol (**5**), 3,3-di(2-fluorenyl)-2-butanone (**6**), 3,3-di(2-fluorenyl)-2-butanol (**7**), *cis*- (**8a**) and *trans*-2,3-di(2-fluorenyl)-2-butene (**8b**), and *meso*- (**9a**) and *dl*-2,3-di(2-fluorenyl)butane (**9b**). The structural proof for these compounds was confirmed by authorized syntheses.

Scheme I



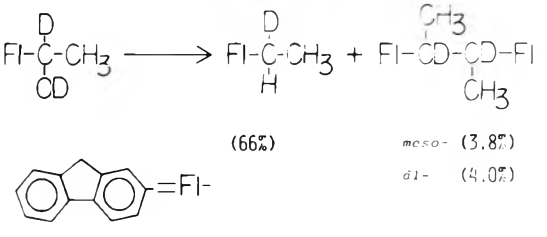
These results suggest, on the grounds of the formation of intermediaries **3** and **4**, that the reduction sequence of **1** may differ somewhat from the conventional concept of the Clemmensen reduction;[9] generally, the reaction cannot proceed through the corresponding carbinol since the carbinol itself is not reduced.

The reduction of **1** gave, in addition to **2**, a pair of cis, trans isomers, **8a** and **8b**, and diastereomers of **9a** and **9b**. The formation of these isomers provides some interesting stereochemical information, because the recent studies of the Clemmensen reduction have rarely observed such abnormal products as these stereoisomers.

Sequence of the Formation of 2-Ethylfluorene (2) by the Clemmensen Reduction of 2-Acetylfluorene (1). The reduction of **1** and its homologues was carried out in xylene using amalgamated zinc and hydrochloric acid according to the method described in *Organic Reactions*.[9] These results are summarized in Table I.

At an initial stage of the reduction, **1** yielded **2, 3, 4, 5, 6, 9a,** and **9b.** Carbinol **3** was also reduced to **2** accompanied by small amounts of **9a** and **9b** as easily as in the case of **1.** The Clemmensen reduction of olefin **4** afforded **2,** but the yield of **2** was smaller than that from **1.** Additionally, the deuteriocarbinol, 2-(α-hydroxyethyl)fluorene-C_α,O-d_2, was converted into 2-ethylfluorene-C_α-d and *meso*- and *dl*-2,3-di(2-fluorenyl)butane-C_2,C_3-d_2 under similar reaction conditions, as Scheme II shows.

Scheme II



These findings are explained by assuming that the carbinol **3** is one of the important intermediates in the Clemmensen reduction of **1.** The sequence of the formation of **2, 3, 4,** and **9** is presumed as Scheme III. Carbinol **3** may be formed from

Scheme III

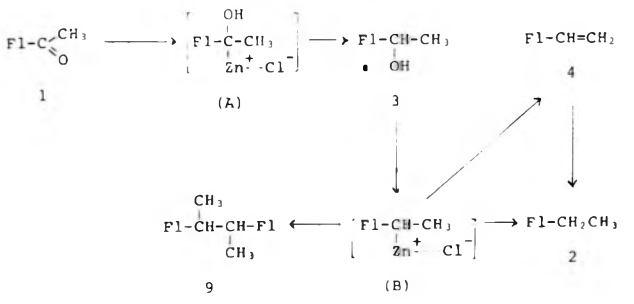


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Table I. Clemmensen Reductions of 2-Acetylfluorene (1) and Its Homologues

Reactant	Reaction time, h	Products, % 2	5	6	8a	8b	9a	9b	Recovd, %
1[a]	0.5	55.2	12.2				0.9	0.7	24.3
1	48	76.3		0.5	1.5	1.2	6.1	5.8	
2	48								97.5
3[b]	48	75.3					4.4	3.6	
4[c]	48	27.5							35.6
5	48	0.8		30.5	18.5	4.2	1.1	2.3	24.8
6[d]	30				2.7	5.4			85.0
7	48				0.6	1.3	0.8	0.7	89.5
8a	48					1.0	1.0		93.4
8b	48				1.9			3.1	93.1
9a	48								92.9
9b	48								95.8

[a] Trace amounts of 3, 4, and 6 were confirmed by ir and VPC. [b] A trace amount of 4 was confirmed by VPC. [c] Low quantity of 2 may be due to the formation of polymeric products.[8] [d] A trace amount of 7 was confirmed by LPC.

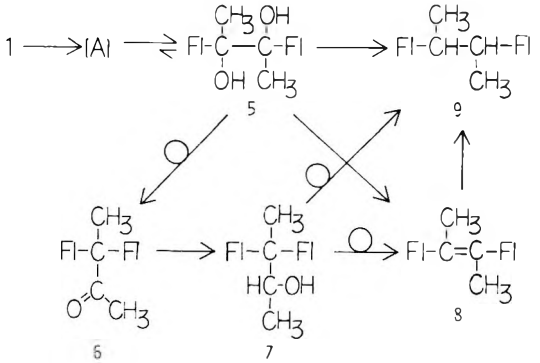
1 through the coordinated ion (A)[10] and 3 is converted easily via another intermediate ion (B) to 2 and 9. An experiment using the deuterio compound would negate the equilibrium between A and B. A part of 2 can be obtained from 4 which is produced via β-hydride transfer of B to 1.

Nakabayashi described,[11] supporting the concept of Brewster,[12] that phenyl methyl carbinol and styrene were not intermediates to ethylbenzene by the Clemmensen reduction of acetophenone, because both were not reduced under the similar conditions. On the other hand, fluorenol and its homologues have been reported[13] to be obtained by the same reduction of the corresponding fluorenones.

The high stability of fluorenol may be due to the steric hindrance of the 1 and 8 positions in fluorenol and the conjugation effects in such a rigid structure, which are much different from those of the mobile structure such as phenyl methyl carbinol. The effects in 3 would be between those of fluorenol and phenyl methyl carbinol.[14]

Dimeric Products by the Clemmensen Reduction of 2-Acetylfluorene (1). The Clemmensen reduction of 1 afforded 5, 6, 7, 8, and 9 as minor products, as shown in Scheme IV.

Scheme IV



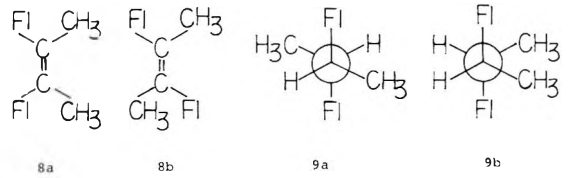
Pinacol 5 may be formed through the coordinated ion A. There is an equilibrium between A and 5 which lies nearly to 5, because a small amount of 2 has been confirmed in the reduction of 5. The pinacol 5 would yield 9, 8, and 6 by reduction, by dehydroxylation, and by pinacol-type transformation with the 2-fluorenyl migration, respectively. Pinacolone 6 is hydrogenated to alcohol 7; 7 gives 8 and 9 by the Wagner–Meerwein (or retropinacol) rearrangement.

The dimeric final product 9 is afforded by reduction of 5 and 8, by the Wagner–Meerwein transformation of 7, and by coupling of the intermediate ion (B) with ion Fl–CH(CH_3)-OH_2^+ and/or with 2-(α-chloroethyl)fluorene[15] (Scheme III).

Formations and Reactions of the Dimeric Compounds. A pair of diastereomers with mp 306–308 °C (9a) and with mp 234–235 °C (9b) were obtained by the Clemmensen reduction of 1. Both isomers were also formed by the reactions of 2-(α-bromoethyl)fluorene (10) with Mg and with $LiAlH_4$ and by treatment of 6 with hydriodic acid in acetic acid. Hydrogenations of 8a and 8b gave 9a and 9b, respectively, by cis addition, analogous to the formation of *meso*- and *dl*-diphenylbutane.[16] The chemical shifts of the methine and methyl protons in the NMR spectrum of 9a are observed at higher fields than those of the isomeric 9b. These findings are consistent with the assignment of 9a to the meso isomer and 9b to *dl*-2,3-di(2-fluorenyl)butane, by similar consideration to diphenylbutane isomers.[17]

Compounds of mp 144–145 °C dec (8a) and of mp 287–288 °C dec (8b) were obtained by reduction of 1 with $TiCl_4$–Zn in dry tetrahydrofuran (THF).[18] Maximum absorption in the uv spectrum of 8b shifts to longer wavelength and the intensity increases compared to 8a. The NMR chemical shift of the methyl groups in 8b appears at higher field than that of 8a. Photochemical isomerization of 8a afforded isomeric 8b. From this evidence, the isomers are assigned to be *cis*- (8a) and *trans*-2,3-di(2-fluorenyl)-2-butene (8b), similar to the case of dimethylstilbene,[19] as shown in Scheme V.

Scheme V



The oxidation of 8a with osmic acid afforded 5 which has also been obtained under a short reduction period of 1 (Table I). The pinacol 5 was obtained by the reaction of di(2-fluorenyl)glyoxal with MeMgI, by photoreduction of 1 in Et_3N–ethanol, and by reductions of 1 with NaOH–Zn and with $TiCl_4$–Zn.[18] Further, 5 gave 1 by $Pb(OAc)_4$ oxidation.

The corresponding pinacolone 6 was given by the reaction of 5 with polyphosphoric acid or H_2SO_4 in acetic acid. The oxidation of 6 yielded 3,3-di(2-fluorenoyl)-2-butanone, di(2-fluorenoyl) ketone,[20] and fluorenone-2-carboxylic acid.[21] Consequently, the pinacolone 6 is established as the compound formed by the migration of the 2-fluorenyl group in 5; the isomer due to methyl group migration is shown to be absent in these experiments.

The hydrogenation of **6** afforded **7**, which gave, of course, **9a** and **9b** by reaction with hydriodic acid.

Experimental Section

All the melting points are uncorrected.

The ir spectra were recorded on a IR-G spectrophotometer (Japan Spectroscopic Co., Ltd.), as KBr pellets. The LPC data were obtained on a FLC-150 liquid-phase chromatograph (Jasco) attached a column JASCOSIL WC-01, using a 1:1 mixture of methylene chloride and isooctane as carrier. The measurements of uv spectra were run with a ORD/UV-5 optical rotatory dispersion recorder (Jasco) at scanning speed of 1.8 s/nm in isooctane.

The NMR spectra were obtained with a JNM-C60HL spectrometer (Japan Electron Optics Laboratory Co., Ltd.), using Me_4Si as internal reference. The VPC analyses were run with a JGC-1100FP gas chromatograph (JEOL), using a 1-m column containing 10% Silicone SE-30 on Chromosorb WAW (80–100 mesh) for dimeric products or a 20-cm column containing 10% PEGA on Diasolid M (80–100 mesh) for monomeric compounds. The mass spectra were measured with a RMU-6E apparatus (Hitachi, Ltd.) by means of a direct inlet system.

Clemmensen Reduction of 2-Acetylfluorene (1) and Its Homologues. General Procedure. Amalgamated zinc was prepared just before its use according to the procedure of Martin[9] from 10 g of zinc turnings, 14 ml of 10% aqueous mercuric chloride, and 1 ml of concentrated hydrochloric acid.

A solution of 0.01 mol of reactant and 200 ml of xylene was refluxed with the foregoing amalgamated zinc and 20 ml of 6 N hydrochloric acid. A 5-ml portion of concentrated hydrochloric acid was added every 6 h during the heating period.

After the mixture was allowed to cool to room temperature, the solution was decanted from any unchanged amalgam, and the residue was washed with a small amount of xylene. The washings and the reaction solutions were combined, and the organic layer was separated from the aqueous layer, washed with water until neutral, dried over calcium chloride (a trace part of it was analyzed by means of VPC and LPC), and evaporated to dryness.

The residue after evaporation was separated and purified by combination of vacuum sublimation, alumina-column chromatography, and recrystallization.

Clemmensen Reduction of 2-(α-Hydroxyethyl)fluorene-C_α,O-d_2. Deuteriocarbinol (100 mg) obtained by $LiAlD_4$ reduction of **1** was treated in the manner described above to give 2-(α-deuterioethyl)fluorene (66%) and trace amounts of *meso*- and *dl*-2,3-dideuterio-2,3-di(2-fluorenyl)butane.

2-Acetylfluorene (1) was synthesized by a method similar to that of Bachmann and Sheehan:[1] yield 92%; mp 131–132 °C (recrystallized from ethanol); ir ($\nu_{C=O}$) 1672 cm^{-1}; NMR (CCl_4) δ 2.50 (s, $-CH_3$), 3.77 (s, $>CH_2$), and 7.12–7.91 ppm (m, aromatic H).

The alcoholic mother liquor gave 2,7-diacetylfluorene:[22] yield 1%; mp 179.5–180 °C; ir ($\nu_{C=O}$) 1672 and 1662 cm^{-1}; mass spectrum *m/e* 250 (M^+), 235, 207, 192, and 165; NMR (benzene-d_6) δ 2.23 (s, 2-CH_3), 3.34 (s, $>CH_2$), and 7.12–7.90 ppm (m, aromatic H).

2-(α-Hydroxyethyl)fluorene (3).[7] The foregoing **1** (25 g) was hydrogenated in benzene (500 ml) using Raney nickel (W-7, 30 g) as a catalyst at room temperature: yield 94%; mp 140–141 °C (from cyclohexane); ir (ν_{OH}) 3320 $cm.^{-1}$

The same carbinol was also obtained by reduction of **1** (5 g) with sodium amalgam (50 g) in ethanol (500 ml), yield 4.4 g (88%).

2-Vinylfluorene (4). A. A finely powdered mixture of 13.9 g of **3**, 3.0 g of $KHSO_4$, and 1.5 g of copper powder was sublimed in vacuo at 180–190 °C, according to the method of Berkovic:[23] yield 5.7 g (45%); mp 137–139 °C; mass spectrum *m/e* 192 (M^+) and 165; NMR[8] (CCl_4) δ 3.64 (s, $>CH_2$), 5.12 (d, *trans*-Fl-C=CH), 5.61 (d, *cis*-Fl-C=CH), 6.63 (q, FlHC=), and 7.00–7.60 ppm (m, aromatic H).

B. A 2.7-g portion of **10** in 40 ml of freshly distilled *N,N*-dimethylformamide was refluxed with 1.3 g of KCN and 1.79 g of CuCN for 24 h, yield 74%.

2-(α-Bromoethyl)fluorene (10). Alcohol **3** (6.3 g) was treated with dry HBr in acetic acid (180 ml) at 20 °C. The deposited material was filtered, washed with water, dried, and recrystallized from hexane to give **10**: yield 6.2 g (76%); mp 99–100 °C dec; NMR (CCl_4) δ 1.98 (d, $-CH_3$), 3.64 (s, $>CH_2$), 5.13 (q, >CH–), and 7.09–7.64 ppm (m, aromatic H).

Anal. Calcd for $C_{15}H_{13}Br$: C, 65.95; H, 4.80. Found: C, 66.12; H, 4.84.

***meso*- and *dl*-2,3-Di(2-fluorenyl)butane (9). A. Grignard Reaction of 10.** A solution of bromide **10** (5.46 g) in 120 ml of THF was added dropwise for 20 min into 80 ml of THF containing magnesium (2.2 g), and the mixture was refluxed for 2 h. The resulting solution was evaporated to dryness and decomposed with dilute hydrochloric acid. The precipitate was sublimed in vacuo at 100 °C to afford 0.50 g (13%) of **2**, mp 99–100°. The unsublimable part was recrystallized from pyridine to give 1.28 g (33%) of **9a**, mp 306–308 °C, and 0.60 g (16%) of **9b**, mp 234–235 °C.

Mass spectrum of **9a** *m/e* 386 (M^+), 369, 205, 193 (base peak), 178, and 165; NMR (pyridine-d_5) δ 1.18 (d, 2-CH_3, J = 6 Hz), 2.98 (m,[24] 2 >CH–), 3.88 (s, 2 $>CH_2$), and 7.12–7.98 ppm (m, aromatic H). Anal. Calcd for $C_{30}H_{26}$: C, 93.22; H, 6.78. Found: C, 93.27; H, 6.53.

Mass spectrum of **9b** *m/e* 386 (M^+), 352, 193 (base peak), 178, and 165; NMR (pyridine-d_5) δ 1.35 (d, 2-CH_3), 3.09 (m,[24] 2 >CH–), 3.71 (s, 2 $>CH_2$), and 7.21–7.98 ppm (m, aromatic H). Anal. Found: C, 93.04; H, 6.90.

B. Reduction of 10 with $LiAlH_4$. Lithium aluminum hydride (0.57 g) suspended in THF (150 ml) was added to a solution of **10** (5.46 g) in THF (100 ml), and the resulting solution was refluxed for 9 h; 0.62 g (16%) of **9a**, 0.93 g (24%) of **9b**, and 0.71 g (18%) of **2** were isolated.

C. Rearrangement of 6. A mixture of **6** (2.0 g), hydriodic acid (1.5 ml), and red phosphorus (1.0 g) in acetic acid (50 ml) was heated for 24 h to give **9a** (0.89 g, 46%), **9b** (0.21 g, 11%), and **6** (0.26 g, 13%). In addition, a trace amount of **7** was confirmed by means of LPC.

2,3-Di(2-fluorenyl)-2,3-butanediol (5). A. Reduction of 1 with Zn–NaOH. A mixture of **1** (10.4 g), ethanol (300 ml), zinc dust (30 g), water (9 ml), and NaOH (20 g) was refluxed for 7 h. The reaction mixture was poured into 2000 ml of water and the organic precipitate was recrystallized from pyridine to afford 5.4 g (52%) of **5**: mp 278–279 °C dec (picrate mp 163–164 °C dec); ir (ν_{OH}) 3550 cm^{-1}; mass spectrum *m/e* 418 (M^+), 384, 369, 357 (base peak), 208, 193, and 165; NMR (Me_2SO-d_6) δ 1.41 (s, 2-CH_3), 3.77 (s, 2 $>CH_2$), 4.85 (s, 2-OH), and 7.07–8.55 ppm (m, aromatic H). Anal. Calcd for $C_{30}H_{26}O_2$: C, 86.09; H, 6.26. Found: C, 86.34; H, 6.26.

Complex with 2,4,7-trinitrofluorenone, mp 224–226 °C dec. Anal. Calcd for $C_{30}H_{26}O_2$·2($C_{13}H_5O_7N_3$): C, 64.12; H, 3.46; N, 8.01. Found: C, 63.83; H, 3.49; N, 8.03.

A mixture of **1** (3.5 g), zinc dust (10 g), NH_4Cl (0.7 g), and water (12 ml) in ethanol (100 ml) was treated in a manner similar to that described above to give **5** (2.2 g, 61%).

B. Reduction of 1 with $TiCl_4$–Zn. Ketone **1** (2.1 g) was reduced according to the direction of Mukaiyama et al.,[18] and gave **5** (1.6 g, 78%).

C. Photoreduction of 1 in Et_3N–Ethanol. Ketone **1** (6.3 g) in a mixture of ethanol (300 ml) and Et_3N (54 ml) was irradiated using a 100-W high-pressure mercury lamp at 53 °C for 2 h in an atmosphere of nitrogen according to the method of Davidson et al.;[25] 4.1 g (65%) of **5** was obtained.

D. Reaction of MeMgI with Di(2-fluorenyl)glyoxal. MeMgI (prepared from 0.25 g of Mg and 1.42 g of MeI in dry ether) was allowed to react with di(2-fluorenyl)glyoxal (300 mg) in dry benzene (60 ml) to yield pinacol **5** (233 mg, 72%).

E. Oxidation of 8a with Osmic Acid. A mixture of **8a** (384 mg), OsO_4 (300 mg), pyridine (0.4 ml), and ether (50 ml) was left for 45 h at room temperature under an inert atmosphere, evaporated to dryness, and chromatographed in benzene on alumina. The black adsorption band on the column was extracted with pyridine. The filtrate was treated with aqueous sodium sulfite to give 0.15 g (36%) of **5**.

Reaction of 5 with $Pb(OAc)_4$. A solution of **5** (0.88 g) and $Pb(OAc)_4$ (1.2 g) in absolute acetic acid (200 ml) was stirred at 29 °C for 3.5 h; 0.71 g (86%) of **1** and 0.07 g (8%) of **5** were obtained.

3,3-Di(2-fluorenyl)-2-butanone (6). A 100-ml portion of acetic acid containing 0.53 g of **5** and 1.3 g of polyphosphoric acid was refluxed for 6 h. After cooling, the reaction mixture was poured into 500 ml of water and the precipitate was purified by means of alumina-column chromatography in benzene and recrystallization from ethanol to afford 0.43 g (86%) of **6**: mp 156–157 °C dec; ir ($\nu_{C=O}$) 1705 cm^{-1}; mass spectrum *m/e* 400 (M^+), 357, 342, 191, 178, 165, and 43; NMR ($CDCl_3$) δ 2.00 (s, $-CH_3$), 2.20 (s, $-COCH_3$), 3.87 (s, 2 $>CH_2$), and 7.08–7.90 ppm (m, aromatic H). Anal. Calcd for $C_{30}H_{24}O$: C, 89.96; H, 6.04. Found; C, 90.25; H, 5.89.

The residue of the filtration of the hot ethanolic solution gave 2,3-di(2-fluorenyl)-1,3-butadiene in 1.5% yield: mp 272–274 °C; mass spectrum *m/e* 382 (M^+), 368, 352, 191, and 165. Anal. Calcd for $C_{30}H_{22}$: C, 94.20; H, 5.80. Found: C, 94.31; H, 5.74.

Oxidation of 3,3-Di(2-fluorenyl)-2-butanone (6). A mixture of **6** (1.0 g) and $KMnO_4$ (11 g) in acetone (70 ml) was refluxed for 2 h to yield 1.04 g (97%) of 3,3-di(2-fluorenoyl)-2-butanone: mp 195–196 °C; ir ($\nu_{C=O}$) 1717 and 1705 cm^{-1}; mass spectrum *m/e* 428 (M^+), 385, 370, and 179; NMR (Me_2SO-d_6) δ 2.05 (s, $-CH_3$), 2.20 (s, $-COCH_3$), and 7.20–7.75 ppm (m, aromatic H). Anal. Calcd for $C_{30}H_{20}O_3$: C, 84.09; H, 4.70. Found: C, 84.20; H, 4.69.

A solution of **6** (2.0 g), sodium dichromate (20 g), a few drops of H_2SO_4, and acetic acid (60 ml) was refluxed for 3.5 h; 0.68 g (35%) of

di(2-fluorenoyl) ketone,[20] mp 298–299 °C, 0.13 g (6%) of 3,3-di(2-fluorenoyl)-2-butanone, mp 195–196 °C, and 0.05 g (2%) of fluorenone-2-carboxylic acid,[21] mp 338 °C dec, were separated.

3,3-Di(2-fluorenyl)-2-butanol (7). Butanone **6** (15.3 g) in benzene (250 ml) was hydrogenated under an atmospheric pressure of hydrogen using Raney nickel catalyst (W-7, 15 g) at room temperature. The reaction mixture was filtered, the filtrate was evaporated to dryness, the residue was recrystallized from cyclohexane, and the crystal was dried in vacuo at 95–105 °C for 10 h to afford 13.5 g (88%) of **7**: mp 134–135 °C dec; ir (ν_{OH}) 3570 cm^{-1}; mass spectrum *m/e* 402 (M^+), 384, 357, 341, and 165; NMR (pyridine-d_5) δ 1.35 (d, $-CH_3$), 1.98 (s, $-CH_3$), 3.75 (s, 2 $>CH_2$), 5.04 (quintet, $>CH-$), 6.05 (d, $-OH$), and 7.13–7.92 ppm (m, aromatic H). Anal. Calcd for $C_{30}H_{26}O$: C, 89.51; H, 6.51. Found: C, 89.31; H, 6.41.

***cis*- and *trans*-2,3-Di(2-fluorenyl)-2-butene (8). A. Reduction of 1 with $TiCl_4$–Zn.** Ketone **1** (2.1 g) was reduced with $TiCl_4$ (2.8 g) and zinc (2.0 g) in THF (100 ml);[18] 1.48 g (76%) of **8a**, mp 144–145 °C dec (from ethanol), and 0.28 g (15%) of **8b**, mp 287–288 °C dec (from pyridine), were obtained.

Mass spectrum of **8a**: *m/e* 384 (M^+, base peak), 369, 354, 218, 203, 193, 191, 179, and 165; NMR (pyridine-d_5) δ 2.23 (s, 2-CH_3), 3.62 (s, 2 $>CH_2$), and 7.02–7.79 ppm (m, aromatic H); uv λ_{max} 271 nm (log ϵ 4.658). Anal. Calcd for $C_{30}H_{24}$: C, 93.71; H, 6.29. Found: C, 93.89; H, 6.19.

Mass spectrum of **8b**: *m/e* 384 (M^+), 369, 354, 192, and 165; NMR (pyridine-d_5) δ 2.11 (s, 2-CH_3), 3.93 (s, 2 $>CH_2$), and 7.07–8.02 ppm (m, aromatic H); uv λ_{max} 278 nm (log ϵ 4.671). Anal. Found: C, 93.84; H, 5.99.

B. Reaction of 7 with H_2SO_4. Carbinol **7** (3.2 g) in benzene (25 ml) containing a few drops of H_2SO_4 was refluxed for 1 h to afford **8b** (2.22 g, 73%).

Hydrogenation of 2,3-Di(2-fluorenyl)-2-butene (8). Cis butene **8a** (100 mg) in benzene (100 ml) was stirred with Raney nickel (W-4, 10 g) at 50 °C for 3 h to give 87.4 mg (87%) of **9a**.

Trans isomer **8b** (500 mg) was treated with Raney nickel (25 g) in the manner described above to yield **9b** (196 mg, 39%) and recovery of **8b** (166 mg, 33%).

Photoisomerization of *cis*-2,3-Di(2-fluorenyl)-2-butene (8a). Cis butene **8a** (226 mg) in benzene (100 ml) was irradiated using a 100-W high-pressure mercury lamp for 18 h; 169 mg (75%) of **8b** was isolated.

Oxidation of *trans*-2,3-Di(2-fluorenyl)-2-butene (8b). A suspension of **8b** (384 mg) in acetone (20 ml) was refluxed with $KMnO_4$ (1.4 g) for 30 h. The reaction mixture was worked up as usual to give 2-acetylfluorenone[26] (186 mg, 41%), mp 160–161.5 °C, 2-(2-fluorenoyl)-3-(2-fluorenyl)-2-butene (9.5 mg, 2%), mp 244–245 °C, 2,3-di(2-fluorenoyl)-2-butene (14 mg, 4%), mp 280–281 °C, and recovery (113 mg, 30%) of **8b**.

Ir of 2-(2-fluorenoyl)-3-(2-fluorenyl)-2-butene ($\nu_{C=O}$) 1706 cm^{-1}; NMR (benzene-d_6) δ 1.90 (s, 2-CH_3), 3.52 (s, $>CH_2$), and 6.96–7.74 ppm (m, aromatic H). Anal. Calcd for $C_{30}H_{22}O$: C, 90.42; H, 5.57. Found: C, 90.27; H, 5.82.

Ir of 2,3-di(2-fluorenoyl)-2-butene ($\nu_{C=O}$) 1710 cm^{-1}; NMR (benzene-d_6) δ 1.70 (s, 2-CH_3) and 7.01–7.62 ppm (m, aromatic H). Anal. Calcd for $C_{30}H_{20}O_2$: C, 87.35; H, 4.89. Found: C, 87.56; H, 4.91.

Friedel–Crafts Reaction of Fluorene with Oxalyl Chloride. A 1.5-g portion of oxalyl chloride was added dropwise to a mixture of fluorene (3.32 g) and $AlCl_3$ (2.0 g) in carbon disulfide (40 ml), and the resulting mixture was refluxed for 1 h.

Upon treatment in an usual manner, the reaction mixture was evaporated to dryness and chromatographed in benzene–ethanol (9:1) on alumina; di(2-fluorenyl)glyoxal (0.47 g, 12%), mp 262.5–263 °C, di(2-fluorenyl) ketone (0.57 g, 16%), mp 281–281.5 °C, and ethyl fluorene-2-carboxylate (0.47 g, 10%), mp 86–87 °C, were isolated.

Ir of di(2-fluorenyl)glyoxal ($\nu_{C=O}$) 1653 cm^{-1}. Anal. Calcd for $C_{28}H_{18}O_2$: C, 87.02; H, 4.69. Found: C, 87.04; H, 4.42.

Ir of di(2-fluorenyl) ketone ($\nu_{C=O}$) 1642 cm^{-1}; mass spectrum *m/e* 358 (M^+), 193, and 165. Anal. Calcd for $C_{27}H_{18}O$: C, 90.47; H, 5.06. Found: C, 90.52; H, 5.07.

Ir of ethyl fluorene-2-carboxylate ($\nu_{C=O}$) 1692 cm^{-1}; mass spectrum *m/e* 238 (M^+), 223, 210, 209, 193, and 165; NMR (CCl_4) δ 1.40 (t, $-CH_3$), 3.82 (s, $>CH_2$), 4.32 (q, $-CH_2-$), and 7.16–8.10 ppm (m, aromatic H). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.34; H, 5.94.

Di(2-fluorenyl) Ketone. The Friedel–Crafts reaction of fluorene (3.2 g) with fluorene-2-carbonyl chloride (4.3 g) using $AlCl_3$ (6.5 g) in carbon disulfide (80 ml) afforded di(2-fluorenyl) ketone, yield 6.4 g (97%), mp 281–281.5 °C.

Oxidation of the ketone with $KMnO_4$ gave di(2-fluorenoyl) ketone[20] (88%), mp 298–299 °C, mass spectrum *m/e* 386 (M^+).

Registry No.—**1**, 781-73-7; **2**, 1207-20-1; **3**, 20371-86-2; **4**, 10473-10-6; **5**, 58473-47-5; **5** complex with 2,4,7-trinitrofluorenone, 58473-48-6; **6**, 58473-49-7; **7**, 58473-50-0; **8a**, 58473-51-1; **8b**, 58473-52-2; **9a**, 58473-53-3; **9b**, 58473-54-4; **10**, 42914-77-2; 2,7-diacetylfluorene, 961-27-3; 2,3-di(2-fluorenyl)-1,3-butadiene, 58473-55-5; 3,3-di(2-fluorenoyl)-2-butanone, 58473-56-6; di(2-fluorenyl) ketone, 55341-69-0; fluorenone-2-carboxylic acid, 784-50-9; 2-acetylfluorenone, 42136-05-0; 2-(2-fluorenoyl)-3-(2-fluorenyl)-2-butene, 58473-57-7; 2,3-di(2-fluorenoyl)-2-butene, 58473-58-8; di(2-fluorenyl)glyoxal, 58473-59-9; di(2-fluorenyl) ketone, 55341-67-8; ethyl fluorene-2-carboxylate, 58473-60-2.

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New and Effective Reagents for 1,4 Reduction of α,β-Unsaturated Ketones, $LiAlH_4$–CuI and Its Reactive Species H_2AlI

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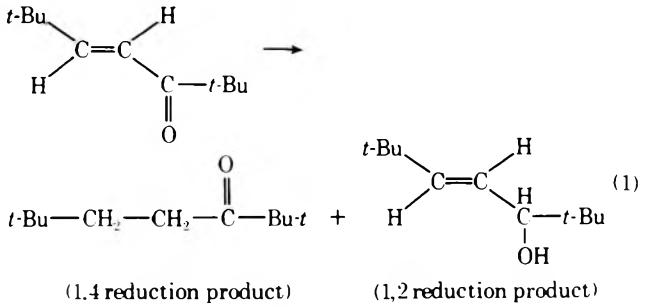
Conjugate reduction of six enones by the new reagent $LiAlH_4$–CuI has been studied. The optimum conditions for conjugate reduction depend on the ratio of $LiAlH_4$:CuI:enone, temperature, solvent, and reaction time involving contact of $LiAlH_4$ and CuI before the enone is added. Enone I can be reduced in quantitative yield and 100% regioselectivity in 1 h or less when the ratio of $LiAlH_4$:CuI:enone is 1:4:1, the solvent is THF, and the temperature is 0 °C. The enones II–VI also can be reduced in high yield and 100% regioselectivity. Reduction of enones I and III with $LiAlH_4$–$TiCl_3$ proceeds with 100% regioselectivity; however, the yields are lower (66 and 34%, respectively) compared to the results obtained with the $LiAlH_4$–CuI reagent. The reagent $LiAlH_4$–$FeCl_3$ was found to be ineffective for conjugate reduction. The new reagents ($LiAlH_4$–CuI and $LiAlH_4$–$TiCl_3$) show different stereoselectivity than $LiAlH_4$ toward 4-*tert*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone. Compared with $LiAlH_4$–CuI, related reagents ($LiAlH_4$–CuCl, $LiAlH_4$–HgI_2, and $LiAlH_4$–$HgCl_2$) show less regioselectivity in enone reduction; however, the reagent AlH_3–CuI is as effective in conjugate reduction as $LiAlH_4$–CuI. H_2AlI has been found to be the reactive species of the reagents $LiAlH_4$–CuI and AlH_3–CuI. The compounds H_2AlX and $HAlX_2$ where X = I, Br, and Cl were synthesized independently and were evaluated as conjugate reducing agents.

Catalytic hydrogenation[1] (H_2–Pd/C) and dissolving metal reduction[2] (Na–aqueous NH_3) are the most common methods for effecting conjugate reduction of enones. The shortcomings of these methods are mainly inconvenience and in many cases low yields. Recently, LiCuRH[3] and KB(*sec*-Bu)$_3$H[4] have been reported as effective reagents for conjugate reduction of enones. However, in the former case the reagent is quite difficult to prepare whereas in the latter case only 1,2 reduction is observed when β substituents are present in the enone. A method of accomplishing conjugate reduction of α,β-unsaturated carbonyl compounds by the use of an easily prepared reagent would indeed be very useful.

It is well known that $LiAlH_4$ favors 1,2 reduction of enones.[5] On the other hand, the reactivity of $LiAlH_4$ can be substantially modified by the addition of metal salts. In this connection $LiAlH_4$–$AlCl_3$[6] has found unusual applicability in epoxide reductions, $LiAl(OCH_3)_3H$–CuI[7] can effect reductive removal of halo and mesyloxy groups, and $LiAlH_4$–$TiCl_3$[8] has been found to be an excellent coupling reagent. Since $LiAlH_4$ is commercially available and convenient to handle as a standardized solution in ether or THF, its ability, in admixture with certain metal halides e.g., CuI, CuBr, CuCl, $TiCl_3$, HgI_2, $HgCl_2$, and $FeCl_3$, to effect conjugate reduction of enones was studied.

Results and Discussion

The enone 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one (enone I) was chosen as a representative enone for this study (eq 1). Reaction products were identified by NMR and compared with authentic samples. Yields were determined by GLC using an internal standard.



(1)

(1,4 reduction product) (1,2 reduction product)

The effect of $LiAlH_4$–CuI on enone I has been studied in detail and the results are shown in Table I. Since $LiAlH_4$ (runs 1 and 2) and $LiAlH_4$–CuI (catalytic amount of CuI, run 3) give mostly 1,2 reduction, the 1,4 reduction product is assumed to arise from a species other than $LiAlH_4$. We have studied a wide variety of stoichiometric ratios of $LiAlH_4$:CuI:enone (runs 4–19) and have found that a ratio of 1:4:1 gives the best results under the conditions that $LiAlH_4$ and CuI are allowed to react before the addition of enone. At this stoichiometric ratio enone I was reduced in quantitative yield and 100% regioselectivity to the conjugate reduction product in THF at 0 °C when the reaction was allowed to proceed for 1 h. Stoichiometry relating the reactive species to ketone is important (runs 14–16) since a significant amount of enone is recovered unreacted when the $LiAlH_4$:CuI:enone ratio is 1:4:4 or 1:4:2. When the $LiAlH_4$–CuI ratio is 1:1 or 1:2 a significant amount of 1,2 product or unreacted ketone or both are observed (runs 4–11).

When $LiAlH_4$ and CuI are mixed at 0 °C in THF a deep black color immediately results with some gas evolution. It was found that ~3 min reaction time is required (runs 17–19) for all of the $LiAlH_4$ to be consumed so that no 1,2 reduction product is observed. Reaction of the active reagent with the enone appears to be over in 30–60 min.

Temperature studies clarify the stability of the $LiAlH_4$–CuI reagent. No reaction between $LiAlH_4$ and CuI occurs at −78 °C (run 26), slow reaction at −20 °C with some 1,2 reduction and recovered enone (run 27), and partial decomposition of the active reagent at room temperature (run 28). When $LiAlH_4$ and CuI were mixed at 0 °C and then cooled to −78 °C, no reaction took place as evidenced by complete recovery of the enone (run 26). On the other hand, generation of the active reagent at 0 °C followed by cooling to −20 °C before enone addition (run 27) resulted in 84% reaction with 100% regioselective formation of the conjugate reduction product. Since 10% ketone was recovered, it is clear that reduction of the substrate at −20 °C has no advantage over reduction at 0 °C. On the other hand, when the reagent was generated at 0 °C and allowed to warm to room temperature, 67% conjugate reduction product was observed with 29% recovery of the ketone. Apparently enough of the reagent decomposes at room temperature that a substantial amount of the starting material is recovered. It appears then, that the optimum temperature for generation of the reagent and addition of the substrate is 0 °C.

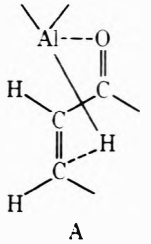
The optimum conditions (1:4:1 stoichiometry, 0 °C, THF) have been applied to other enones (III, IV, V, and VI). The yields are generally high and the regioselectivity is 100%. However, the slower reaction rate for cis enone II and the

Table I. Reduction of Enones with $LiAlH_4$–CuI in THF

Expt	Enone	Molar ratio: $LiAlH_4$	CuI	Enone[a]	Temp, °C	Enone, % recovered	Products, %: 1,4	1,2
1	*t*-BuCH=CHC(=O)-*t*-Bu trans (I)	1.0	0	4.0	0	12	3	83
2	I	1.0	0	1.0	0	0	0	99
3	I	0.42	0.01	1.0	0	0	7	92
4	I	1.0	1.0	2.0[c]	0	0	40	50
5	I	1.0	1.0	1.0	0	0	64	27
6	I	1.0	1.0	0.5	0	0	49	~44
7	I	1.0	2.0	4.0[c]	0	54	46	6
8	I	1.0	2.0	2.0[c]	0	6	81	9
9	I	1.0	2.0	2.0[c,d]	0	0	58	34
10	I	1.0	2.0	2.0[c]	RT	62	38	<1
11	I	1.0	2.0	1.0	0	0	95	6
12	I	1.0	2.0	0.5	0	0	82	~1
13	I	1.0	3.0	1.0	0	0	87	7
14	I	1.0	4.0	4.0	0	69	26	0
15	I	1.0	4.0	4.0[e]	0	20	21	59
16	I	1.0	4.0	2.0	0	21	69	0
17	I	1.0	4.0	1.0[c]	0	0	82	7
18	I	1.0	4.0	1.0[f]	0	0	69	16
19	I	1.0	4.0	1.0	0	0	99	0
20	I	1.0	4.0	1.0[d]	0	0	78	20
21	I	1.0	4.0	1.0[c]	RT	0	63	24
22	I	1.0	4.0	1.0	RT	47	34	<1
23	I	1.0	4.0	4.0	−30	47	38	7
24	I	1.0	4.0	1.0	−20	0	88	11
25	I	1.0	4.0	1.0	−78	0	0	93
26	I	1.0	4.0	1.0	0 → −78[g]	101	0	0
27	I	1.0	4.0	1.0	0 → −20[g]	10	84	0
28	I	1.0	4.0	1.0	0 → RT[h]	29	67	~1
29	cis (II)	1.0	4.0	1.0	0	33	40	0
30	$(CH_3)_2C$=CHC(=O)CH_3 (III)	1.0	4.0	1.0	0	3	66	~1
31	III	1.0	4.0	0.5	0	8	70	0
32	CH_3CH=C(CH_3)C(=O)CH_3 (IV)	1.0	4.0	1.0	0	0	97	0
33	CH_3CH=CHC(=O)CH_3 (V)	1.0	4.0	1.0	0	0	78	0
34	PhCH=CHC(=O)Ph (VI)	1.0	4.0	1.0	0	0	101	0

[a] Product is based on ketone used. Reaction time for all reactions is 30–60 min, counted from ketone addition. [b] All reaction mixtures were stirred for 3 min between $LiAlH_4$ addition and ketone addition, except when noted. [c] $LiAlH_4$ was added rapidly, stirred for 1 min, then the ketone added dropwise. [d] Et_2O was used instead of THF. [e] $LiAlH_4$ was added to the ketone–CuI mixture. [f] Same as *c*, but interval was 10 s. [g] $LiAlH_4$ was added at 0 °C, ketone was added at −78 or −20 °C. [h] Stirred at RT for 10 min before ketone addition.

observation of no reaction with cyclohexenone and 3,3,5-trimethylcyclohexenone suggests to us a mechanism involving



A

a six-center transition state (A). It is more difficult for the rigid cyclohexenone systems, cis enones, and trans enones possessing disubstitution at the *β* carbon of the enone to accommodate such a transition state (A) and hence these kinds of compounds should react more slowly.

Reduction of enones I and III (Table II) with $LiAlH_4$–$TiCl_3$ was found not to be as effective as reduction with $LiAlH_4$–CuI. As might have been expected, the most effective ratio of $LiAlH_4$:$TiCl_3$ was different from that found for $LiAlH_4$–CuI. Also one might expect that the optimum reaction temperature would be different since the reactive titanium species would

Table II. Reduction of Enones with $LiAlH_4$–$TiCl_3$ in THF

		Molar ratio						Products, %	
Expt	Enone	$LiAlH_4$	$TiCl_3$	Enone	Temp, °C	Reaction time	Enone recovered	1,4	1,2
35	I	2.0	1.0	1.0	0	1 h	0	12	70
36	I	1.0	1.0	1.0	0	1 h	0	13	53
37	I	1.0	2.0	1.0	0	1 h	0	46	24
38	I	1.0	3.0	1.0	0	1 h	0	29	34
39	I	1.0	1.0	1.0	RT	10 min	0	53	0
40	I	1.0	1.0	1.0	RT	30 min	0	63	0
41	I	1.0	1.0	1.0	RT	1 h	0	58	0
42	I	1.0	1.0	1.0	RT	1.5 h	0	55	0
43	I	1.0	1.0	1.0	RT	12 h	0	53	0
44	I	2.0	2.0	1.0	RT	1 h	0	66	0
45	I	2.0	1.0	1.0	RT	1 h	0	63	0
46	I	2.0	1.0	1.0	Reflux	1 h	0	60	0
47	I	4.0	4.0	1.0	RT	8 h	0	46	0
48	I	1.0	2.0	1.0	RT	1 h	0	29	~1
49	I	1.0	2.0	1.0	RT	8 h	0	35	0
50	I	1.0	2.0	1.0	RT → 0[g]	1 h	0	35	~1
51	I	3.0	4.0	1.0	RT	1 h	0	18	25
52	I	1.0	3.0	1.0	RT	1 h	0	14	0
53	I	3.0	1.0	1.0	RT	1 h	0	28	41
54	I	2.0	2.0	1.0[f]	RT	10 min	0	6	31
55	III	1.0	1.0	1.0	RT → 0[g]	1 h	~1	34	0
56	III	1.0	2.0	1.0	RT → 0[g]	1 h	~2	18	0
57	III	2.0	2.0	1.0[f]	RT	1 h	0	33	0
58	III	2.0	2.0	1.0[f]	RT	1 h	9	0	25

[f] Same as *f* in Table I but 60 min.

Table III. Reduction of Enone I with $LiAlH_4$–HgI_2, $LiAlH_4$–$HgCl_2$, or $LiAlH_4$–CuCl in THF

	Molar ratio			Temp,	Enone recovered,	Products	
Expt	$LiAlH_4$	HgI_2	Enone	°C	%	1,4	1,2
59	1.0	1.0	1.0	0	0	65	22
60	1.0	1.5	1.0	0	0	86	8
61	1.0	2.0	1.0	0	0	93	5
62	1.0	4.0	1.0	0	75	8	0
		$HgCl_2$					
63	1.0	1.0	1.0	0	0	46	56
64	1.0	1.5	1.0	0	42	32	17
		CuCl					
65	1	4	1	0	55	32	4

be expected to have different stability and different reactivity characteristics compared to the copper reagent. It appears that optimum results are obtained using a $LiAlH_4$:$TiCl_3$:enone ratio of 1:1:1 at room temperature for 30 min (yield 63%). Lower reaction temperatures (0 °C) for enone I produced a substantial amount of 1,2 reduction product and a wide variation in reactant stoichiometry and reaction time seemed to have either little or adverse effect on the desired results.

Reduction of enone III with $LiAlH_4$–$TiCl_3$ was correspondingly slower than that observed for $LiAlH_4$–CuI. The best conditions of stoichiometry, temperature, and reaction time were similar to that observed for enone I except that the yields were lower (~33%).

$LiAlH_4$ was allowed to react with $FeCl_3$ at −78 °C, 0 °C, and room temperature followed by addition of enone I. In no case did the enone react.

Two other metal salts, HgI_2 and $HgCl_2$, were also admixed with $LiAlH_4$ (Table III). The regioselectivity was dependent on the ratio of $LiAlH_4$:HgX_2 and also on the halide. When the metal halide was changed from HgI_2 to $HgCl_2$ the unusual regioselective is lost corresponding to the same trend observed when the salt is changed from CuI to CuCl.

Since $LiAlH_4$–CuI and $LiAlH_4$–$TiCl_3$ produced a species in solution different than either of the reactants, and gave 100% regioselectivity, it was decided to evaluate these reagents as stereoselective reducing agents. Both $LiAlH_4$–CuI and $LiAlH_4$–$TiCl_3$ were allowed to react with 4-*tert*-butylcyclohexanone (VII) and 3,3,5-trimethylcyclohexanone (VIII) in THF. The results of Table IV show that both reagents give considerably more equatorial attack compared to $LiAlH_4$ and that the $LiAlH_4$–$TiCl_3$ reagent gives considerably more equatorial attack compared to the $LiAlH_4$–CuI reagent on both ketones.

The unusual effectiveness of the reagent $LiAlH_4$–CuI for conjugate reduction of the enones encouraged us to study the nature of this reagent in solution. We found that the reactive intermediate is H_2AlI and not CuH or $CuAlH_4$.[9] Equation 2 explains the observation of a black precipitate and gas evolution when this reaction is carried out. The compound H_2AlI was synthesized independently and was found to produce the same results as observed with $LiAlH_4$–CuI (1:4) (run 75). Actually, after most of these studies were complete, we found that the 1:4 ratio of $LiAlH_4$–CuI is not necessary. When the mixing period for $LiAlH_4$ and CuI was changed from 3 to 20 min (runs 11 and 73) we found that the enone was reduced in 98 and 100% regioselectivity.

$$LiAlH_4 + 2CuI \rightarrow H_2AlI + LiI + Cu^\circ + H_2 \qquad (2)$$

Since H_2AlI was found to react just as the reagent $LiAlH_4$–CuI, it was decided to evaluate other halogenoaluminum hydrides. We prepared[10] the series H_2AlI, $HAlI_2$, H_2AlBr, $HAlBr_2$, H_2AlCl, and $HAlCl_2$ expecting that for steric reasons the $HAlX_2$ compounds would be more regioselective than the H_2AlX compounds and that the regioselectivity of the reduction would decrease as the steric requirement of the hydrogen decreases (I > Br > Cl). It is clear from Table V that indeed the iodo compounds are more selective than the bromo or chloro compounds and that $HAlX_2$ compounds are also highly regioselective. However, owing to the steric requirement of $HAlI_2$ the reaction with enone I is much slower com-

Table IV. Stereoselective Reduction of 4-*tert*-Butylcyclohexanone (VII) or 3,3,5-trimethylcyclohexanone (VIII) with $LiAlH_4$–CuI and $LiAlH_4$–$TiCl_3$ in THF

Expt	Ketone	Molar ratio $LiAlH_4$	Molar ratio CuI (or $TiCl_3$)	Molar ratio Ketone	Conditions	Ketone recovered, %	Rel yield, % ax OH	Rel yield, % eq OH	Mass balance
67	VII	1.5	0	1.0	0 °C, 2 h	0	8	92	~100
68	VII	1.0	4.0 (CuI)	1.0	0 °C, 1 h	0	29	71	~100
69	VII	1.0	1.0 ($TiCl_3$)	1.0	RT, 1 h	0	70	30	81
70	VIII	1.5	0	1.0	0 °C, 2 h	0	80	20	~100
71	VIII	1.0	4.0 (CuI)	1.0	0 °C, 1 h	0	85	15	~100
72	VIII	1.0	1.0 ($TiCl_3$)	1.0	RT, 1 h	0	97	3	74

Table V. Reduction of Enone I with the Reagents $LiAlH_4$–CuI, AlH_3–CuI, H_2AlI, $HAlI_2$, H_2AlBr, $HAlBr_2$, H_2AlCl, and $HAlCl_2$ in THF

Expt	Molar ratio			Conditions	Enone, % recovered	Products, % 1,4	Products, % 1,2
	$LiAlH_4$	CuI	Enone[b]				
73	1	2	I	0 °C, 15 min	0	98	0
	AlH_3	CuI	Enone[b]				
74	1	3	I	0 °C, 15 min	0	99	<1
	H_2AlI	CuI	Enone[b]				
75	1	0	1	0 °C, 1 h	0	98	<0.5
76	1	0	1[d]	0 °C, 1 h	0	70	12
77	1	~10	1	0 °C, 1 h	77	11	0
	$HAlI_2$	CuI	Enone				
78	1		1	0 °C, 1 h	84	0.5	0
79	2		1	RT, 4 h	33	59	5
80	4		1	RT, 1 h	15	80	2
	H_2AlBr	CuI	Enone				
81	1		1	0 °C, THF, 1 h	0	86	12
	$HAlBr_2$	CuI	Enone				
82	1		1	0 °C, THF, 1 h	0	92	6
	H_2AlCl	CuI	Enone				
83	1		1	0 °C, 10 min	0	86	15
	$HAlCl_2$	CuI	Enone				
84	2		1	0 °C, 1 h	8	86	7

[d] Et_2O solvent. [b] The mixing period of $LiAlH_4$–CuI or AlH_3–CuI was 20 min before enone addition.

pared to H_2AlI and hence $HAlI_2$ is not as attractive a reagent. Because $HAlI_2$ reacts so slowly the regioselectivity suffers slightly probably owing to the small equilibrium amount of AlH_3 expected in THF solutions of $HAlI_2$.

Experimental Section

Materials and Techniques. Manipulations of air-sensitive compounds were performed under nitrogen in a glove box equipped with a recirculating system described elsewhere.[11] THF and Et_2O were distilled from $NaAlH_4$ and $LiAlH_4$, respectively, prior to use. $LiAlH_4$ solutions were prepared by refluxing $LiAlH_4$ (Alfa Inorganics) in THF for at least 24 h followed by filtration through a fritted glass funnel in a box. The clear solution was standardized for aluminum content by EDTA. CuI (Fisher) was purified by dissolving it in saturated potassium iodide solution followed by treatment with decolorizing charcoal, filtration, and precipitation by dilution with water. The purified CuI was collected and washed with absolute EtOH and dry Et_2O in the drybox. Anhydrous ferric chloride (Fisher sublimed) titanium trichloride (Alfa), mesityl oxide (Eastman), 4-*tert*-butylcyclohexanone (Friton), 3,3,5-trimethylcyclohexanone (Chemical Samples Co.), and enones IV, V, and VI (Aldrich) were used without further purification. 2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one [sublimed, 45 °C (5–10 mmHg)] was prepared as previously described.[12] Mercuric iodide and chloride were dried by heating at 90–100 °C under vacuum for 4 h and standard THF solutions of these salts were prepared in the drybox. The reagent H_2AlI was obtained by adding I_2–THF solution to AlH_3–THF at <0 °C. The resulting solid was then filtered and washed carefully with THF.[10] The $HAlI_2$, H_2AlCl, and $HAlCl_2$ reagents were prepared by following literature methods.[10] The ratio of H:Al was satisfied for each haloalane within experimental error.

Reduction Procedure. A 10-ml Erlenmeyer flask with a Teflon coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen flush. CuI, CuCl, $TiCl_3$, or $FeCl_3$ (ca. 2 mmol) was transferred to the flask in the drybox; it was sealed with a rubber septum, removed from the box, and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil filled bubbler. THF or Et_2O solvent (4 ml) was introduced into the reaction vessel and temperatures regulated by ice–water (0 °C), dry ice–acetone (−78 °C), or dry ice–carbon tetrachloride (−20 °C). A known concentration of $LiAlH_4$ solution was then added to the slurry. On addition a deep black color is immediately produced with gas evolution except in the case of CuI at −78 °C. After an indicated period, enone with internal standard, n-$C_{12}H_{26}$, was added dropwise. After the designated reaction time the reaction mixture was quenched with a minimum of distilled water and the resulting solution dried over $MgSO_4$. Analysis of the product and yield data was obtained by GLC, using a 15-ft 10% Carbowax 20M on Chromosorb W. Authentic samples were used to identify the retention times of the 1,4 and 1,2 reduction products.

Reduction of 4-*tert*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone was carried out by a similar procedure as described for the enone. Product yields were also determined by GLC.

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Registry No.—I, 20859-13-6; II, 29569-89-9; III, 141-79-7; IV, 565-62-8; V, 625-33-2; VI, 94-41-7; VII, 98-53-3; VIII, 873-94-9; $LiAlH_4$, 16853-85-3; AlH_3, 7784-21-6; H_2AlI, 58602-50-9; $HAlI_2$, 58602-51-0; H_2AlCl, 14644-71-4; $HAlCl_2$, 13497-97-7; CuI, 7681-65-4; $TiCl_3$, 7705-07-9; HgI_2, 7774-29-0; $HgCl_2$, 7487-94-7; CuCl, 7758-89-6.

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A Study of the Stork Reductive Cyclization of Steroidal Acetylenic Ketones in Aprotic Media with the Naphthalene Anion Radicals

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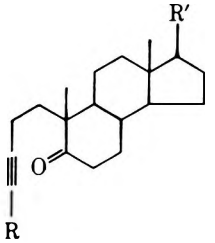
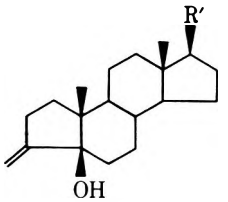
Reductive cyclization of steroidal acetylenic ketones was achieved in THF or DME with $C_{10}H_8{}^-M^+$. From 4,5-secocholest-3-yn-5-one (**1a**) the allylic alcohol 3-methylene-*A*-norcholestan-5β-ol (**2a**) is the sole product. With this reagent no overreduction occurs. Recovery of starting material was proved to be due to competitive enolate ion formation. Ratio of reductive cyclization to recovery varied with solvent and counterion as well as with substrate. In a series of 4,5-secocholestan-5-ones the substituent at 10α was varied from $-(CH_2)_2C{\equiv}CH$ (**1a**) and $-(CH_2)_2CH_2C{\equiv}CH$ (**25**) to $-(CH_2)_2C{\equiv}C-CH_3$ (**1c**). The observed ratios were 2.3, 8.2, and 0.7, respectively. In each case, the cyclization was regiospecific leading exclusively to an exo double bond. Kinetic control was established when **25** showed the same stereoselectivity as the others and gave an A:B cis product. The formation of different products from **25** and **1c** eliminated allene intermediates. With **1c** the stereochemistry of addition across the acetylene was syn:anti equal to 52:48. This shifted to >80% syn for **5e**. Based on available data, a mechanism is proposed. Electron is transferred preferentially, though reversibly, by $C_{10}H_8Na$ to the ketone group to give a ketyl radical ion. In the next slow step, this attacks the acetylene intramolecularly, as a radical and not as a nucleophile. Equilibration of the resulting vinyl radical with its isomer precedes reduction and protonation to the allyloxy anion precursor of the cyclized product. The initial addition across acetylene is syn. This follows from the change in syn:anti ratio to 70:30 when **1c** is added to excess reducing agent.

The reductive cyclization of γ-ethynyl ketones to allylic alcohols with alkali metals in liquid ammonia was first reported by Stork.[1] In a slightly modified form, this reaction was used for making interesting *A*-nor sterols.[2] The reaction was found to be stereoselective. Thus, the only products obtained from 4,5-secocholest-3-yn-5-one (**1a**) were 3-methylene-*A*-norcholestan-5β-ol (**2a**) and 3-methyl-*A*-norcholest-3-ene (**3a**). The latter was a product of overreduction. With NH_4Cl as a proton source, **3a** was the only product. With *t*-BuOH under carefully controlled conditions, mixtures of **2a** and **3a** resulted. Even under these conditions, **1b** gave only **3b**.

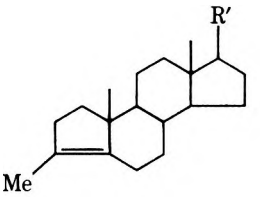
It was expected that overreduction could be avoided with a milder reducing agent used in combination with an aprotic medium. When preliminary work[3] indicated that naphthalene sodium in THF could serve the purpose, a deeper study into several aspects of this reaction was undertaken and is the subject of the present report.[4]



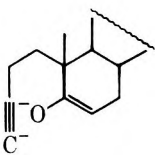
1a, R = H; R′ = C_8H_{17}
b, R = H; R′ = OH
c, R = Me; R′ = C_8H_{17}



2a, R′ = C_8H_{17}
b, R′ = OH
c, R′ = OMe



3a, R′ = C_8H_{17}
b, R′ = OH



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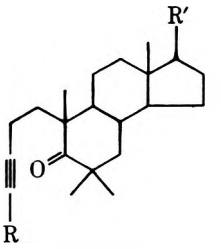


5a, R = H; R′ = C_8H_{17}
b, R = H; R′ = OH
c, R = H; R′ = OMe
d, R = Me; R′ = C_8H_{17}
e, R = D; R′ = C_8H_{17}

A solution of the acetylene ketone **1a** in THF or DME was

titrated with the dark green concentrated solution (0.6 N) of the naphthalene radical anion ($C_{10}H_8\cdot^-$, M^+) in THF or DME to a faint green end point. Each mole of sterol **1a** required 2.0 ± 0.2 mol of reagent and gave 70% **2a** and 30% **1a**. It was a very clean reaction amenable to semiquantitative evaluation. Hence the effect on the yield of changes in counterion and solvents could be studied. The results are given in Table I.

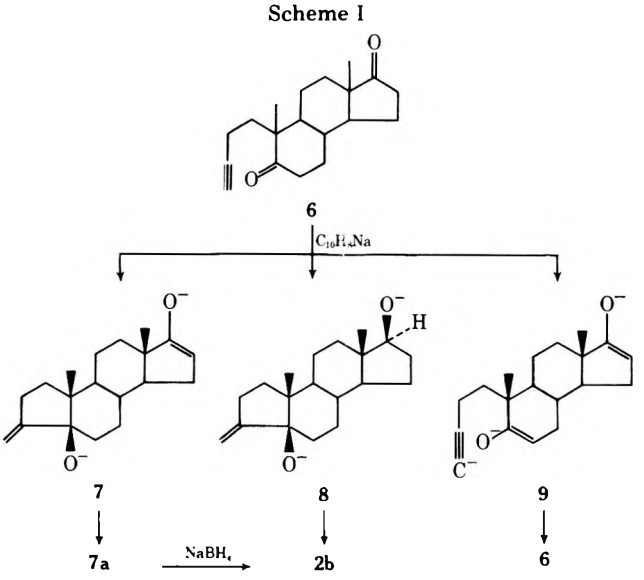
Electron transfer from sodium using naphthalene as a catalyst could also be achieved leading to formation of **2a** in 90% yield. However, the reaction was much slower. Details of the catalytic use of naphthalene are given in the Experimental Section. The rest of this article is concerned only with the very fast reactions which took place on titration with preformed reagent. The yields of **2a** were not noticeably affected by reversing the mode of addition or by lowering the temperature to 0 °C.

Recovery of 30% starting material could be reconciled with consumption of 2 mol of reagent by taking into account the dual behavior of the aromatic radical ions first noted by Scott.[5] They reduce halides by electron transfer but the same reagents act exclusively as strong bases when they react with alcohols. It was obvious that this dual behavior is being demonstrated in a 7:3 ratio with the steroidal substrate. Proton abstraction leads to dianion **4** which regenerates starting material on workup. Formation of the enolate ion was confirmed by adding excess methyl iodide prior to workup. In this case, **2a** was accompanied by the 6,6-dimethyl derivative **5a**[7] to the exclusion of **1a**. The removal of proton from acetylene was confirmed by quenching with deuterioacetic acid.

Reductive cyclization with $C_{10}H_8Na$ was carried out successfully with three distinct types of acetylene ketones. In every case, stereochemistry was established and has yielded information having a significant bearing on the mechanism of this reaction.

Terminal γ-Ethynyl Ketones. Results with **1a** are given in Table I. The 17β-hydroxy compound **1b** was of special interest since it had given only the overreduction product **3b** under protic conditions.[2] With naphthalene sodium **2b** was the only product but separation from **1b** was not possible. Addition of methyl iodide prior to workup gave **2c** and **5c**.[8] The desired **2b** was more conveniently obtained starting from the acetylene dione **6** as shown in Scheme I. All these cyclizations were stereoselective, leading to A:B cis products, and regiospecific, giving only a five-membered ring.

Scheme I



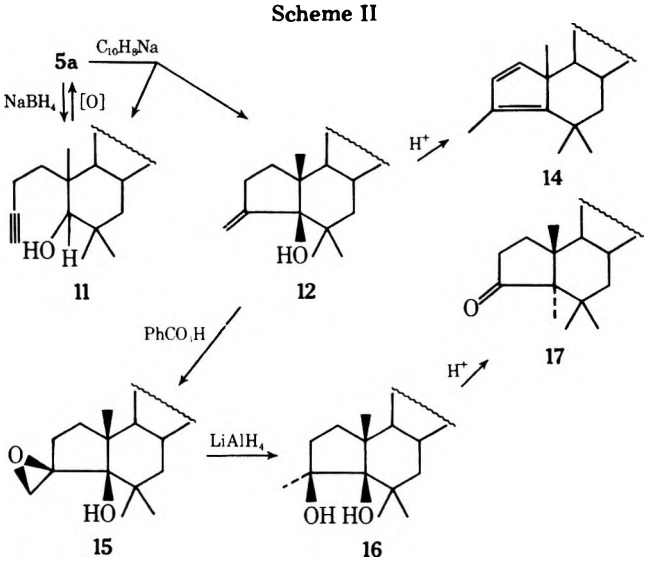
Cyclization of the 6,6-dimethyl derivative **5a** was of interest in view of steric hindrance at and nonenolizability of the ketone group. Reaction of **5a** with $C_{10}H_8Na$ gave 60% **12** and 40% **11**.[9] The latter could also be obtained by borohydride reduction of **5a**. The structure and stereochemistry of **12** were determined as shown in Scheme II.[10] The stereochemistry of **12**

Table I. Effect of Solvent and Counterion on the Reaction of 1a with $C_{10}H_8\cdot^-$

Counter-ion	Solvent[a]	2a	1a[b]	Counter-ion	Solvent[a]	2a	1a[b]
K^+	THF	69[c]	30	K^+	DME	64[c]	35
Na^+	THF	69	27	Na^+	DME	65	31
Li^+	THF	42	45	Li^+	DME	38	50

[a] 0.6 N reagent was used. [b] Recovery via enolate ion **4**. [c] Percentage yields are given based on weights of material isolated by column chromatography.

Scheme II



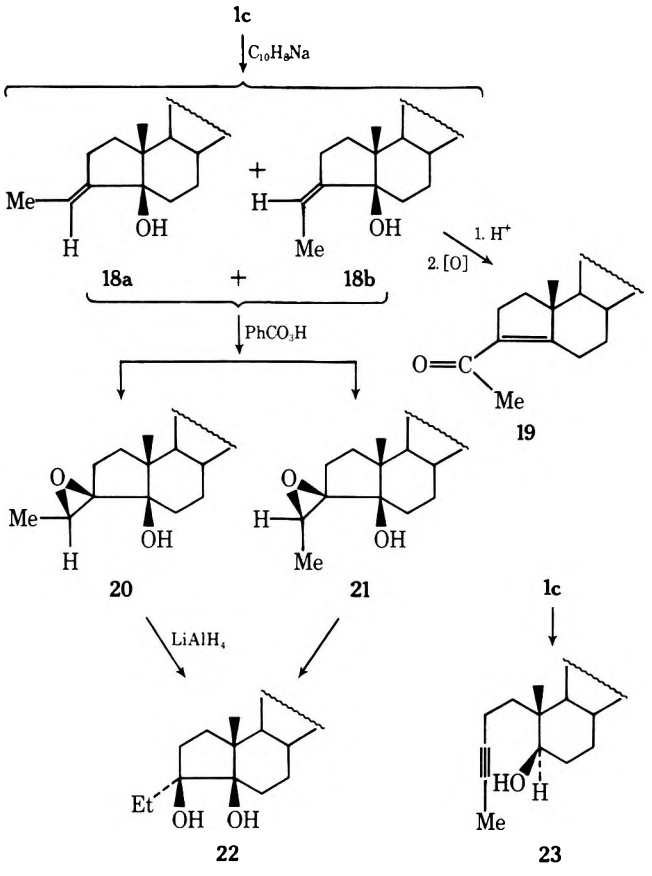
was indicated by NMR to be the same as in **2a** but was independently confirmed since substitution so close to the reacting center could have altered it. The proof consists of stereospecific conversion to **17** having an A:B trans junction as confirmed by its "negative Cotton effect".[11] In this cyclization, there was no recovery of starting material, lending support to the view that survival of ketone from reductive cyclization or reduction is due to enolate ion formation.

The possibility of determining the stereochemistry of addition across the acetylene was opened up by a comparison of the NMR of **12** and **2a**. The exocyclic methylene in the former gave two broad singlets at δ 4.98 and 5.25 whereas the latter gives a multiplet at δ 5.1 ppm. The deshielding of one of the exo protons in the dimethyl series was particularly marked in the epoxidation products. In the NMR of **15** the two protons were at δ 2.75 and 3.48 as compared to δ 2.96 and 3.00, respectively, in the unmethylated compound.[2]

The deshielding is ascribed to steric compression[12] since models showed close proximity of the α-methyl at C-6 to the exo hydrogen cis to C-5. This information was put to use by replacing the acetylenic hydrogen in **5a** by deuterium to give **5e** prior to reductive cyclization. The deuterated **12** produced in this reaction was analyzed by NMR for deuteration at the vinylic position. It could be estimated that 0.8–0.75 atoms of deuterium were present at the exo position cis to C-2, while 0.0–0.2 were at the position cis to C-5. Even this approximate estimation allows the conclusion that, in this case, addition across the acetylene is predominantly syn. The other product of this reaction, **11**, was free from deuterium. The significance of the finding is discussed below.

Nonterminal γ-Ethynyl Ketones. The methyl acetylene ketone **1c** was prepared from 4-methylcholest-4-en-3-one and treated with $C_{10}H_8Na$ to give only two spots on TLC. One corresponded to starting material but addition of methyl iodide prior to workup led to its conversion to the 6,6-dimethyl derivative **5d.** The other spot had an R_f value quite distinct from that of **23** (the major borohydride product of **1c**). It represented a mixture of two compounds obtained in 42% yield. These (**18a** + **18b**) could not be separated but structure and configuration could be assigned on the basis of work summarized in Scheme III.

Scheme III

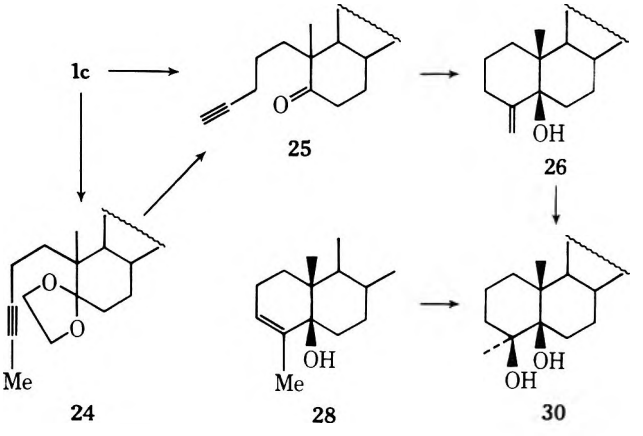


The spectral evidence for the structure of **19** was quite conclusive. Conversion of **20** and **21** individually to the same diol **22** on $LiAlH_4$ reduction established that the stereochemistry at the A:B ring junction was the same in **18a, 18b, 20, 21** and **22.** NMR comparison of these with closely related compounds of established structures[2] with particular reference to the chemical shift of the 19-methyl confirmed that the A:B ring junction must be cis in all. Hence **18a** and **18b** must be stereoisomeric around the double bond. It was essential to determine the relative amounts of the two isomers and if possible their stereochemistry. Since epoxidation yields were quantitative, it could be assumed that information about the relative amounts of **20** and **21** could be extrapolated back. Since **20** and **21** could be separated, it was possible to establish that the isomeric alcohols **18a** and **18b** were in the proportion of 58(±3):42(±3). Thus, *substantial quantities* of both isomers are being produced. Hence there is only marginal preference for syn or anti addition across the acetylene in this case. This significant finding is not dependent on correct assignment of configuration to **18a** and **18b.** A tentative assignment is possible because the methyl doublet in **21** can be expected to be downfield relative to that in **20** because of steric compression. The major isomer has this doublet at δ 1.28 in the NMR whereas the minor one has it at δ 1.50 ppm. Hence, it can be tentatively concluded that syn addition across the acetylene to give **18a** is marginally preferred to anti addition giving **18b.**

The reaction is, however, regiospecific in that no six-membered ring formation is detected.[13] Compound **1c** was converted into the borohydride reduction product **23** on the one hand and the ketal **24** on the other. Both of these were subjected independently to reductive cyclization conditions to obtain evidence for acetylene reduction. They were both quantitatively recovered.

Terminal δ-Ethynyl Ketone. The homologous acetylene ketone **25** was required for distinguishing between kinetic and thermodynamic control. It was made by isomerization of **1c.** The isomerization was carried out by $NaNH_2$ generated in situ by bubbling NH_3 gas into $C_{10}H_8Na$ in THF[14] till the color was discharged. The THF was replaced by toluene and then refluxed. Yields of the rearranged product **25** were not satisfactory. Suspecting fragmentation, we protected the ketone as the ketal **24** prior to isomerization. The yield of **25** improved. Cyclization of this with $C_{10}H_8Na$ gave 89% **26** and 11% **25.** The structure **26** is consistent with spectral data whereas its stereochemistry was established by direct correlation[15] as shown in Scheme IV. The diol **30** is identical with one of the

Scheme IV



two cis diols obtained by the action of OsO_4 on 4-methylcholest-4-ene.

The cyclization of **25** is highly stereoselective giving exclusively an A:B cis product. In common with the other systems, it also shows regiospecificity.

Discussion

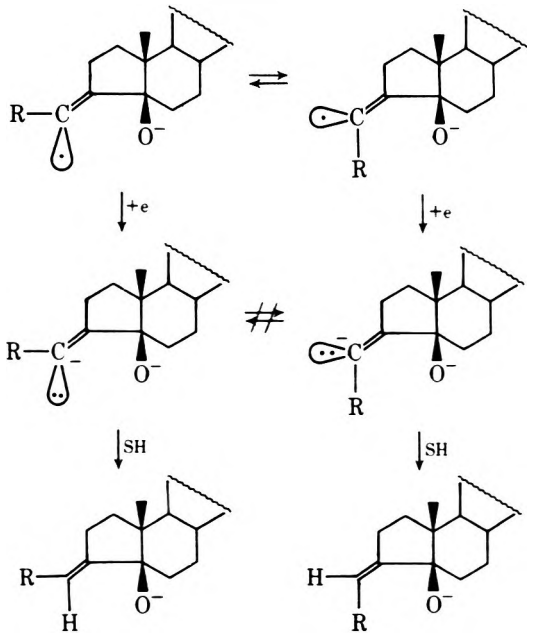
From the preparative point of view, the reductive cyclizations reported here are extensions of the reaction discovered by Stork. The present reagent offers several advantages, the foremost being that no overreduction takes place. The stereochemical findings give an insight into the mechanism and are hence briefly summarized here. Reductive cyclization of the 5-keto sterols invariably gave an A:B cis junction with the double bond exo to ring A. The stereochemistry of addition across the acetylene could be studied in only two cases. The disubstituted γ-ethynyl compound **1c** gave a mixture of syn and anti addition in the ratio of 58(±3):42(±3). With the terminal 6,6-dimethyl derivative **5e** the estimation was less accurate but syn addition was not less than 80% and may be higher. The incoming hydrogen comes in syn in spite of the fact that, in the final product, it is under considerable steric compression.

Any mechanism that seeks to explain the transformation of an acetylene ketone to an allyloxy anion has to consider the sequence of addition of two electrons and a proton or one electron and a hydrogen atom. The species produced at each stage, particularly the ones prior to and following the C–C

bond formation, have to be identified. In an aprotic medium proton abstraction is restricted to the relatively nonacidic solvent and to the substrate itself. The mechanism under these conditions need not be the same as the mechanism in liquid ammonia. Observation of the same stereoselectivity does imply some similarities, but, because of the doubt, data from liquid ammonia studies are used here only in a supplementary sense.

It is possible to cut across many possibilities because the result of reaction of **1c** strongly favors the intermediacy of a cyclized vinyl radical. The formation of substantial amounts of both isomers **18a** and **18b** from **1c** taken in conjunction with the shift towards syn addition observed with **5e** is best accounted for in terms of the equilibrium shown in Scheme V.[16]

Scheme V



Equilibration is expected to be almost complete because of the temperature[17] and the mode of addition. Conversion of the two vinyl radicals to the corresponding carbanions followed by protonation by solvent accounts for the products. Since vinyl carbanions are not expected to equilibrate under the reaction conditions[16b] the ratio of the isomeric carbanions is expected to be retained in the protonated product in spite of the considerable steric compression under which the newly introduced proton finds itself in one of the isomers.

The cyclized vinyl radical contains only one electron more than the substrate. Hence, cyclization must occur after one electron has been transferred to the acetylenic ketone. Since electron transfers are often reversible, the question arises as to whether the cyclization step is also reversible and that only the vinyl carbanion formation and protonation is irreversible. This point was settled by the formation of A:B cis compound exclusively in the reaction of **25**. By analogy with 4-keto steroids,[18] the A:B trans isomer of **26** should be stable relative to **26** and hence reversibility at the cyclization stage should have yielded at least some trans compound. In *A*-nor sterols the cis junction is more stable. However, since the environment of the ketone in **1a, 1b, 1c,** and **25** is identical, it is reasonable to conclude that kinetic control is operating in all cases leading to a 5β-ol derivative.

The distinctly different compounds isolated in the reaction of **25** and **1c** form the basis of another useful conclusion. Allenes are not being formed in spite of the strong base present.[19] The above two compounds should give the same allene. If this had occurred, then either starting material recovered or products formed in one set should have been contaminated with the other set. This did not happen nor was any allene detected.

It follows that *either* the acetylene *or* the ketone receives an electron (or alkali metal atom) from the reagent and the resulting radical ion attacks the other uncharged functional group. For the reductive cyclizations using metal and liquid ammonia, Stork has tentatively proposed that the acetylene radical ion is formed followed by nucleophilic attack on the ketone. Lansbury has questioned this interpretation[20] and believes that a nucleophilic attack on the acetylene by the radical ion formed from the ketone is more probable. The latter explanation requires that exclusive anti addition should take place across the acetylene.[21] The data for the aprotic cyclization are contrary to this expectation.

The crucial consideration is whether there is a substantial preference for electron transfer to one of the two functional groups. Preferential attack on the ketone would be expected from reduction potentials.[22] However, in solution, such considerations may not be entirely valid in view of the observations reported in an excellent paper on reduction of acetylenes by House.[17] Formation of species such as –C(Na)=C– is easier than would be anticipated on the basis of reduction potentials. Both ketones and isolated acetylenes (but not acetylides) are reduced by the blue solutions of alkali metals in ammonia or in HMP.[17] Since the alkali metal naphthalenes are much less powerful reducing agents, it was hoped that with these, evidence of selectivity might be obtained. Several studies are reported in the literature on use of these reagents for reduction of diaryl and monoaryl acetylenes[23] but no studies on isolated acetylenes or ketones are reported[24] except for an interesting study on δ-keto esters.[25]

The question of whether the acetylene was capable of accepting an electron from naphthalene sodium in THF was resolved by attempting the reduction of the alcohol **23** and the ketal **24**. These consumed 1.0 ± 0.2 and 0.0 ± 0.2 mol of the reagent only and were quantitatively recovered.[26] The dialkyl acetylene was chosen because failure to reduce a terminal acetylene could have been ascribed to proton abstraction leading to an acetylide ion incapable of reduction. The possibility that carbanion formation by abstraction of a proton from the carbon adjacent to the above acetylene is also ruled out by the titration values as well as the total recovery.

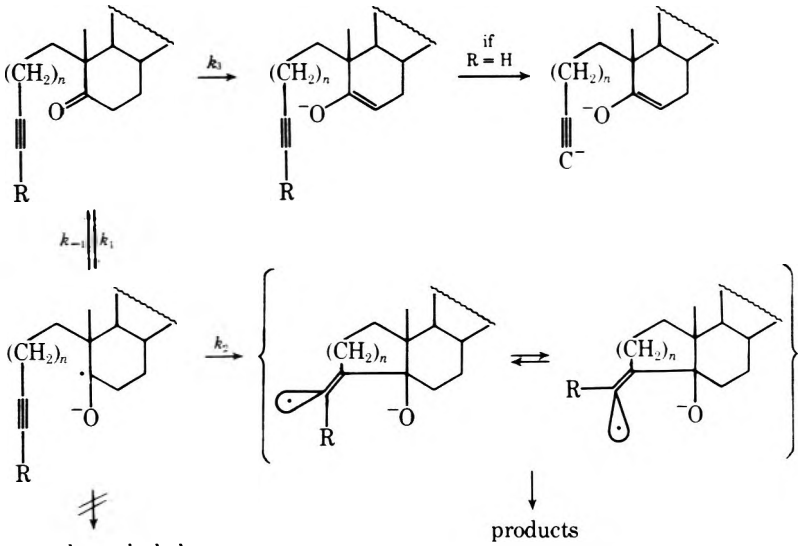
In contrast to the acetylene, the nonenolizable ketone **5a** reacts completely giving the reductively cyclized product **12** and the reduced alcohol **11**. The behavior of the enolizable ketones in **6** is illustrated by Scheme I which ascribes the apparent recovery of some of the ketones to enolate ion formation. It follows that none of the ketones escape attack by the reagent.

The conclusion that the ketone accepts electrons in preference taken in conjunction with the findings discussed below leads to the proposal given in Scheme VI.

Here k_1 and k_3 represent rates of two simultaneous reactions between the same two reactants. Since both reactions involve the 5-keto group, the immediate environment of which is identical in **25, 1a,** and **1c**, the ratio k_1:k_3 would be expected to be nearly the same for these three compounds. In the event of k_1 representing a slow rate-determining step for product formation the ratio of product to recovery should have been the same for **25, 1a,** and **1c**. The actual ratios are, however, 8.2, 2.3, and 0.7, respectively. Thus the slow step in product formation must be k_2, which involves a C–C bond formation, with the ratios apparently reflecting the factors affecting the cyclization step. The equilibrium in the preceding step involves electron transfer. These are known to be fast and are certainly faster than proton abstraction.[27]

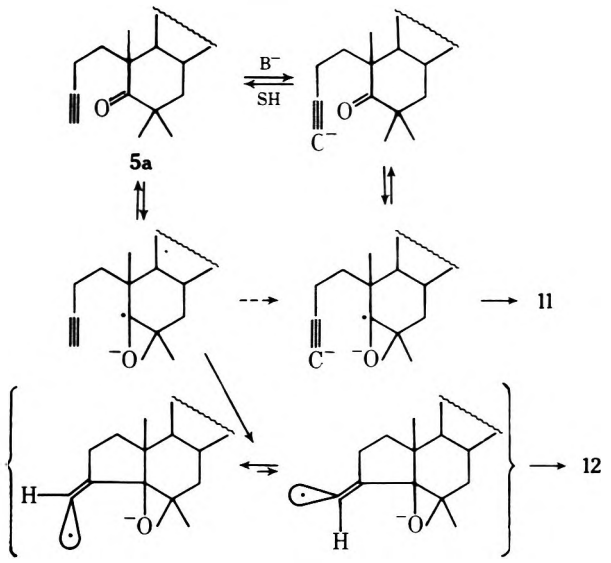
Scheme VII is an extension of Scheme VI to a hindered nonenolizable ketone. Only in this case is the uncyclized 5

Scheme VI



$n = 1, R = H$ **2a** from **1a**
$n = 1, R = CH_3$ **18a** + **18b** from **1c**
$n = 2, R = H$ **26** from **25**

Scheme VII



hydroxy compound formed. This is accounted for by making the reasonable assumption that the rate of cyclization of the fully substituted hindered ketone is much less than in the nonhindered series. The rate of acetylide formation then becomes competitive. Radical cyclization at the acetylide ion is not expected. Hence the intermediate is diverted to the alcohol. This is borne out by deuteration studies. The deuterated **5e** in which the hydrogen attached to the sp carbon has been replaced by deuterium gives the undeuterated alcohol **11**. By the same token product 12 derived from this compound should have been 100% monodeuterated. However, 20–25% undeuterated compound was produced indicating that some reversal of acetylide formation must be occurring by proton abstraction from solvent.

In all the above cases a remarkable regiospecificity was observed. The exo olefins were formed exclusively. Intramolecular radical attack on acetylenes to give exclusively exo products has been reported.[28] A possible explanation for the observed regiospecificity may be that the transition state for cyclization may resemble starting material. Overlap of the orbital at C-5 with a p orbital on one of the sp carbons could lead to an incipient ring. In the larger of the two possible incipient rings the other sp carbon has to be accommodated within the ring whereas in the smaller incipient ring the sp carbon would be outside. Hence sufficient energy differences should exist so that the endo olefins, in six- or seven-membered rings, do not form in competition with the exo olefins.[29]

One interesting aspect of the mechanism is that, except for dimerization and reduction to dianion, there are no proven analogies for radical trapping of a radical ion. Because of this, the possibility that protonation at the oxygen precedes cyclization was considered. Proton abstraction from the substrate cannot account for the yield of 89% in the cyclization of **25** and the amount of naphthalene sodium consumed. So proton abstraction from solvent was the remaining possibility. A test of this was required under similar conditions. Assuming that the anion of cholesterol would be a stronger base than the above radical ion,[27] cholesterol was treated with $C_{10}H_8M$ under the conditions of the above experiments and excess methyl iodide was added subsequently. The amount of cholesteryl methyl ether produced indicated the minimum amount of alcohol that failed to abstract proton from the solvent. This was concentration, solvent, and counterion dependent. The results are given in Table II. Proton abstraction is very little with $C_{10}H_8K$ in DME. Yet yields in cyclization are quite high as seen in Table I. Hence prior protonation does not appear to be a condition for cyclization.[30]

Whereas a satisfactory picture has emerged about the mechanism of the reductive cyclization, the same is not true about the effect of solvent and counterion on this reaction which is summarized in Table I. The limited data can only be amenable to a highly speculative interpretation. A plausible one, conductive to further testing, is herein offered. The slight superiority of THF over DME could be due to the encroachment of proton catalyzed cyclization occurring to a small extent in the former but not the latter, the proton being provided by the solvent. Data in Table II show that this occurs more readily in THF than DME. The significant drop in yields of cyclization with naphthalene lithium solutions as compared to sodium and potassium ones could be due to the former being superior at proton abstraction thereby giving an increased rate of enolate ion formation and hence more recovery of starting material. Naphthalene lithium is in fact preferred over the others for a number of reactions involving proton abstraction from carbon.[31] The actual species involved is not

Table II. Variations in Yield of Methyl Ether of Cholesterol[a]

Reagent	$Li^+Nap\cdot^-$, THF		$Li^+Nap\cdot^-$, DME		$Na^+Nap\cdot^-$, THF		$Na^+Nap\cdot^-$, DME		$K^+Nap\cdot^-$, THF		$K^+Nap\cdot^-$, DME	
Normality	0.60	0.35	0.70	0.41	0.70	0.40	0.75	0.45	0.71	0.50	0.78	0.56
% ether[b]	38	30	83	59	43	33	91	78	58	45	96	89

[a] Cholesterol was titrated with $C_{10}H_8M$ in DME/THF and after decolorization, excess methyl iodide was added. [b] This value is based on cholesteryl methyl ether isolated by column chromatography. The other component was cholesterol. Total material accounted for was 95 ± 3%.

Table III. Catalytic Effect of Naphthalene on Reaction of Sodium[a] with 1a in THF/DME

Solvent	Catalyst[b]	2a	3a	1a	Solvent	Catalyst[b]	2a	3a	1a
THF	0.0 mol	38[c]	6	50	DME	0.0 mol	43[c]	8	41
THF	0.2 mol	72		23	DME	0.2 mol	83		11
THF	0.4 mol	80		15	DME	0.4 mol	90		6

[a] Slow reaction, time 5.5 h. [b] Moles of catalyst relative to 1 mol of 1a. [c] Percentage yields.

known but the dianion formed by disproportionation of $C_{10}H_8Li$ is a strong candidate.

Experimental Section

General. Infrared spectra were obtained with a Perkin-Elmer Model 21 double beam spectrophotometer. Uv spectra were recorded on a Beckman DB spectrophotometer. NMR spectra were obtained with a Varian A-60 spectrometer in CCl_4 or $CDCl_3$ with Me_4Si as internal standard. Optical rotations were determined in chloroform at room temperature with a Carl-Zeiss Winkel spectropolarimeter. Melting points were determined on a standard melting point apparatus and are uncorrected. THF or DME were purified for all purposes by refluxing initially with sodium or with KOH and alumina followed by another distillation from $C_{10}H_8Na$. In all cases, standard grade alumina was used for chromatographic separation unless otherwise stated.

All reactions as well as column chromatography were followed by TLC using microslides with detection by exposure to iodine vapors. Unless otherwise stated, the reactions were worked up as follows. The mixtures were poured into water and extracted twice with ether, and the combined ether extract was washed with dilute HCl followed by water till neutral and dried over anhydrous sodium sulfate.

Preparation and Estimation of Naphthalene Sodium. In a thoroughly cleaned and dry 250-ml two-necked flask was taken 100 ml of freshly purified THF or DME. This was stirred magnetically and 9.6 g (75 mmol) of freshly crystallized and dried naphthalene was added under nitrogen atmosphere. Freshly cut sodium (2.9 g, 130 mmol) was added to this solution in relatively small pieces maintaining throughout a positive nitrogen atmosphere. The solution became green in about 15 min and stirring continued for 3 h thereafter. A narrow-mouthed bent glass tube connected with a buret was then inserted below the surface of the reagent. The buret was flushed with nitrogen and kept under nitrogen atmosphere and could be filled with the reagent by application of greater pressure of nitrogen on the surface of the reagent in the flask. Titrations and reactions were carried out by addition under nitrogen atmosphere to a magnetically stirred solution of sterol. This reagent was estimated by addition to a solution of 386 mg (1 mmol) of cholesterol in 4 ml of THF till the solution became faint green. It was observed that 1.6 ml of the reagent was consumed indicating that a 0.6 N solution had been obtained. This was found to be reproducible over several experiments. Exactly identical procedure was followed for preparing $C_{10}H_8Li$ and $C_{10}H_8K$.

The following experiment describes in detail the use of this reagent for reductive cyclization. The same procedure was followed for all other reductive cyclizations, the only difference being that excess methyl iodide was added prior to workup when trapping of the enolate was desired.

Reductive Cyclization of 4,5-Secocholest-3-yn-5-one (1a) with Naphthalene Sodium. Solution of naphthalene sodium was added under nitrogen atmosphere to a well-stirred solution of 384 mg (1 mmol) of 1a in 5 ml of THF at room temperature till a faint green end point. It was found that 2.1 mmol of the reagent was required. The faint color discharged by itself in about 10 min after turning off nitrogen. The reaction mixture was worked up in the usual way and chromatographed on alumina. Sufficient pentane was used to elute all the naphthalene. Use of benzene/pentane gave 104 mg of the unreacted material followed by 263 mg of 3-methylene-*A*-norcholestan-5β-ol (2a). On crystallization from aqueous methanol this had mp 57–58°; $[\alpha]D$ +20° (c 0.12) (lit.[2] mp 58°, $[\alpha]D$ +20°). It was identical with an authentic sample in its ir and NMR.

The yields of 2a were not noticeably affected by reversing the mode of addition or by lowering the temperature to 0 °C.

The reductive cyclization of 1a was carried out in an identical fashion using DME as solvent. The result of this experiment as well as those with $C_{10}H_8K$ and $C_{10}H_8Li$ in THF and DME are given in Table I.

Reductive Cyclization of 1a with Na in THF/DME with and without Naphthalene. To 384 mg (1 mmol) of 1a in 8 ml of THF or DME 92 mg (4 mg-atoms) of Na metal and specific amounts of naphthalene were added and stirred at room temperature for 5.5 h under a nitrogen atmosphere. No green color was observed throughout the experiment except for a faint green color on the metal surface. The solution was then filtered to remove sodium and washed with dry ether and from the combined filtrates solvent was removed under vacuum to leave a residue which was chromatographed. The results are given in Table III. The yields of 1a, 2a, and 3a are based on the actual weights of the compounds obtained on chromatography.

Naphthalene Sodium/Methyl Iodide on 1a (Trapping of Enolate Ion). A stirred solution of 384 mg (1 mmol) of 1a in 5 ml of DME was titrated to a faint green end point with a DME solution of naphthalene sodium and immediately 0.08 ml (1.3 mmol) of methyl iodide in 4 ml of DME was added and the mixture stirred for 10 min. It was then poured into water and extracted with ether after neutralizing. The ether extract was washed with sodium thiosulfate solution and then with water and finally dried over anhydrous sodium sulfate. Removal of ether under vacuum and chromatography as usual gave 128 mg of an oily material which was formulated as 6α,6β-dimethyl-4,5-secocholest-3-yn-5-one (5a). It has $[\alpha]D$ −3° (c 0.13); ir (CCl_4) 3305 (≡CH), 2110 (–C≡C–), 1690 cm^{-1} (C=O); NMR (CCl_4) δ 0.76 (3 H, s, C-18 methyl), 1.03, 1.04, and 1.06 (C-19 and C-6 methyls). Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.13; H, 11.43.

This was followed by 235 mg of cyclized alcohol 2a.

Similar results were obtained when DME was replaced by THF. Disubstitution at the 6 position was confirmed by NMR of 11 and its acetate in both of which the C-5 H is a singlet.

6α,6β-Dimethyl-4,5-secocholest-3-yn-5ε-ol (11). To a solution of 410 mg (1 mmol) of acetylenic ketone 5a in 8 ml of methanol was added 185 mg (5 mmol) of $NaBH_4$ in one portion. The reduction was complete in about 4 h; 10% acetic acid was added dropwise till the solution became slightly acidic. This was then extracted with ether and washed with a solution of sodium bicarbonate and then with water. The ether was dried over anhydrous sodium sulfate and then distilled off under vacuum to yield a thick mass which was chromatographed on alumina. Elution with 1:1 hexane–benzene gave 20 mg of an oil. It had $[\alpha]D$ +2° (c 0.11); ir (CCl_4) 3590 (OH), 3310 (≡CH), 2120 cm^{-1} (C≡C). It was not further characterized.

Further elution gave 350 mg of the crystalline 6α,6β-dimethyl-4,5-secocholest-3-yn-5ε-ol (11). This had mp 76–77 °C when crystallized from methanol: $[\alpha]D$ +4° (c 0.13); ir (CCl_4) 3580 (OH), 3310 (≡CH), 2120 cm^{-1} (C≡C); NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 0.95 (9 H, s, C-19 and C-6 methyls), 3.08 (1 H, s, C-5 H). Anal. Calcd for $C_{29}H_{50}O$: C, 84.07; H, 12.08. Found: C, 83.87; H, 12.26.

Reduction with $LiAlH_4$ in ether gave the same compound.

Acetylation of **11** with acetic anhydride in refluxing pyridine gave the corresponding acetate in quantitative yield. It had mp 68 °C; $[\alpha]D$ −20° (c 0.12); ir (CCl_4) 3400 (≡CH), 2150 (C≡C), 1770 cm^{-1} (C=O); NMR (CCl_4) δ 0.73 (3 H, s, C-18 methyl), 0.96 (9 H, s, C-19 and C-6 methyls), 2.10 (3 H, s, $-OCOCH_3$), 4.5 (1 H, s, C-5 H). Anal. Calcd for $C_{31}H_{52}O_2$: C, 82.50; H, 11.40. Found: C, 82.27; H, 11.21.

Oxidation of 412 mg of **11** with CrO_3 and pyridine in CH_2Cl_2 overnight at room temperature gave 350 mg of **5a**.

Naphthalene Sodium on 17β-Hydroxy-4,5-secoandrost-3-yn-5-one (1b). Following the literature[2] procedure **1b** was synthesized and 288 mg of it was treated with naphthalene sodium as described above. Chromatography yielded 260 mg of a mixture of **1b** and **2b** as judged by ir and NMR. Various attempts to separate the mixture failed. The mixture could be estimated to contain 55% **2b** by NMR.

Naphthalene Sodium/Methyl Iodide on 17β-Hydroxy-4,5-secoandrost-3-yn-5-one (1b). Titration of a solution of 288 mg (1 mmol) of **1b** in 5 ml of DME followed by addition of 0.25 ml (4 mmol) of methyl iodide after workup and chromatography gave 117 mg of 6α,6β-dimethyl-17β-methoxy-4,5-secoandrost-3-yn-5-one (**5c**). It had $[\alpha]D$ −3° (c 0.10); ir (CCl_4) 3305 (≡CH), 2120 (C≡C), 1692 (C=O), 1450, 1385, 1370, 1100, 1030 cm^{-1}; NMR (CCl_4) δ 0.75 (3 H, s, C-18 methyl), 1.0, 1.03, and 1.08 (C-19 and C-6 methyls), 3.28 (3 H, s, $-OCH_3$). Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.15; H, 10.12.

Further elution with benzene–pentane gave 139 mg of crystalline 3-methylene-17β-methoxy-*A*-norandrostan-5β-ol (**2c**). It had mp 151–152 °C when crystallized from methanol; $[\alpha]D$ + 21° (c 0.12); ir (CCl_4) 3580 (OH), 890 cm^{-1} (=CH_2); NMR (CCl_4) δ 3.25 (3 H, s, $-OCH_3$), 4.98 (2 H, m, =CH_2). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.94; H, 10.51. Found: C, 78.80; H, 10.40.

Preparation of 4,5-Secoandrost-3-yne-5,17-dione (6). To a stirred solution of 4 ml of pyridine in CH_2Cl_2 was added 400 mg of chromium trioxide. To this 400 mg of **1b** in 5 ml of CH_2Cl_2 was added and left overnight. The reaction mixture was worked up to yield after chromatography 380 mg of 4,5-secoandrost-3-yne-5,17-dione (**6**). It had mp 118–120 °C; ir (Nujol) 3315 (≡CH), 2125 (C≡C), 1740 and 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.89 (3 H, s, C-18 methyl), 1.10 (3 H, s, C-19 methyl). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.92; H, 8.87.

Naphthalene Sodium on 4,5-Secoandrost-3-yne-5,17-dione (6). A solution of 286 mg (1 mmol) of acetylenic diketone 6 in 4 ml of THF was titrated with naphthalene sodium in THF. Workup and chromatography on alumina gave 65 mg of the unreacted starting material, followed by 130 mg of 3-methylene-*A*-norandrostan-5β-ol-17-one (**7a**). It had $[\alpha]D$ +20° (c 0.11); ir (CCl_4) 3550 (OH), 1740 (C=O), 900 cm^{-1} (=CH_2). The last fraction gave 68 mg of the cyclized diol **2b**. It had mp 188 °C; $[\alpha]D$ +22° (c 0.13) [lit.[2] mp 188–189 °C, $[\alpha]D$ +22° (c 0.12)], and had ir and NMR identical with that of an authentic sample.

Sodium borohydride reduction of **7a** gave **2b**.

Naphthalene Sodium on 6α,6β-Dimethyl-4,5-secocholest-3-yn-5-one (5a). Preformed naphthalene sodium in DME was added to 205 mg (0.5 mmol) of the above acetylenic ketone **5a** in 3 ml of DME till a faint green end point. By estimation, it was found that 0.9 mmol of the reagent was consumed. The reaction mixture was worked up as usual and chromatographed on alumina. Elution with pentane, after removal of naphthalene, gave 123 mg of 3-methylene-6α,6β-dimethyl-*A*-norcholestan-5β-ol (**12**). It was crystallized from aqueous methanol. It had mp 49–51 °C; $[\alpha]D$ +8° (c 0.14); ir (CCl_4) 3610 (OH), 900 cm^{-1} (=CH_2); NMR (CCl_4) δ 0.71 (3 H, s, C-18 methyl), 1.06, 1.13 (C-19 and C-6 methyls), 4.98 (1 H, s), and 5.25 (1 H, s) (=CH_2). Anal. Calcd for $C_{29}H_{50}O$: C, 84.07; H, 12.08. Found: C, 83.97; H, 11.90.

Further elution gave 79 mg of **11** identical in all respects with the borohydride reduction product reported earlier.

Similar experiments with naphthalene sodium in THF added to 410 mg (1 mmol) of **5a** in 5 ml of THF gave after workup and chromatography 238 mg of **12** and 162 mg of **11**.

For the sake of comparison, the reductive cyclization of **5a** was attempted by the liquid ammonia procedure. A solution of 410 mg (1 mmol) of the dimethyl acetylenic ketone **5a** in 8 ml of THF was added to 20 ml of liquid ammonia. To the stirred mixture was added 69 mg (3 mg-atoms) of freshly cut sodium, followed by 1.5 ml of dry *t*-BuOH. After 6 min, the reaction was quenched by adding methanol. Ammonia was evaporated and the ether soluble portion was chromatographed on silica gel. Elution with hexane gave 370 mg of an oil. It had NMR ($CDCl_3$) δ 0.73 (3 H, s, C-18 methyl), 1.03, 1.1, 1.26 (C-19 and C-6 methyls), 1.78 (3 H, s, C-3 methyl). On the spectral evidence it is tentatively formulated as 3,6α,6β-trimethyl-*A*-norcholest-3-ene (**13**).

3,6α,6β-Trimethyl-*A*-norcholesta-1,3-diene (14). To a solution of 207 mg of 6α,6β-dimethyl tertiary alcohol **12** in 20 ml of acetone was added 28 mg of *p*-toluenesulfonic acid and the mixture was stirred under nitrogen atmosphere. The starting material completely disappeared in about 30 min. Workup and chromatography over alumina gave 185 mg of 3,6α,6β-trimethyl-*A*-norcholesta-1,3-diene (**14**). It was crystallized from chloroform–methanol and had mp 76–77 °C; $[\alpha]D$ 0°; uv λ_{max} (EtOH) 245 nm (ε 3800); ir (CCl_4) 2860, 1460, 1380, 1360 cm^{-1}; NMR (CCl_4) δ 0.66 (3 H, s, C-18 methyl), 0.80, 1.04, 1.16 (C-19 and C-6 methyls), 2.0 (3 H, s, C-3 methyl), 5.9 and 6.1 (2 H, AB q, J = 5.5 Hz). Anal. Calcd for $C_{29}H_{48}$: C, 87.88; H, 12.12. Found: C, 87.49, H, 11.90.

β-Epoxide of 3-Methylene-6α,6β-dimethyl-*A*-norcholestan-5β-ol (15 from 12). To 206 mg of the tertiary allylic alcohol **12** was added 10 ml of 0.77 N perbenzoic acid in chloroform and the mixture was kept overnight at 5 °C. The solution was extracted with $CHCl_3$ after dilution with water and washed with solutions of potassium iodide, sodium thiosulfate, sodium bicarbonate, and finally water. The $CHCl_3$ extract was dried by passing over anhydrous sodium sulfate and concentrated in vacuo. Crystallization from aqueous acetone gave 120 mg of the epoxide **15**. It had mp 163–164 °C; $[\alpha]D$ +4° (c 0.13); ir (CCl_4) 3590 (OH), 1465, 1380, 912 cm^{-1}; NMR (CCl_4) δ 0.73 (3 H, s, C-18 methyl), 1.04 (9 H, s, C-19 and C-6 methyls), 2.75 and 3.48 (2 H, AB q, J = 5 Hz). Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.93; H, 11.62. Found: C, 80.68; H, 11.40.

Another crop (45 mg) of **15** was obtained from the mother liquor.

3α,6α,6β-Trimethyl-*A*-norcholestane-3β,5β-diol (16). To a solution of 215 mg of the epoxy alcohol **15** in 20 ml of dry ether was added 500 mg of $LiAlH_4$ and the mixture was refluxed for 3 h. A saturated solution of aqueous sodium potassium tartarate was added slowly and the product was ether extracted. Removal of ether under vacuum gave 150 mg of an oily material which was crystallized from aqueous methanol. It was formulated as 3α,6α,6β-trimethyl-*A*-norcholestane-3β,5β-diol (**16**). It had mp 95 °C; $[\alpha]D$ +13° (c 0.14); ir (CCl_4) 3510 (OH), 1460, 1380, 1090, 1030 cm^{-1}; NMR (CCl_4) δ 0.74 (3 H, s, C-18 methyl), 1.06, 1.11 (C-19 and C-6 methyls), 1.6 (3 H, s, C-3 methyl). Anal. Calcd for $C_{29}H_{52}O_2$: C, 80.56; H, 12.04. Found: C, 80.21; H, 11.71.

5α,6α,6β-Trimethyl-*A*-norcholestan-3-one (17). To 216 mg of the diol **16** was added 16 ml of 5% methanolic HCl and the mixture was refluxed for about 15 min. The reaction mixture was cooled, neutralized by adding dilute bicarbonate solution, and extracted with ether. Ether was removed under vacuum and the resulting residue chromatographed on alumina. Elution with 1:1 hexane–benzene gave 165 mg of 5α,6α,6β-trimethyl-*A*-norcholestan-3-one (**17**). Crystallization from aqueous methanol gave mp 68–70 °C; $[\alpha]D$ −43° (c 0.10); ir (CCl_4) 1760 cm^{-1} (C=O); NMR (CCl_4) δ 0.71 (3 H, s, C-18 methyl), 1.08, 1.10 (C-19, C-5, and C-6 methyls); $[\alpha]_{365}$ −306°, $[\alpha]_{436}$ −125°, $[\alpha]_{546}$ −58°, $[\alpha]_{578}$ −49°, $[\alpha]_{589}$ −45°. Anal. Calcd for $C_{29}H_{50}O$: 83.99; H, 12.15. Found: C, 83.68; H, 12.00.

Deuterium Exchange on 6α,6β-Dimethyl-4,5-secocholest-3-yn-5-one. A solution of 412 mg of dimethyl acetylenic ketone **5a** in NaOD–D_2O (prepared by adding a few pieces of sodium to D_2O) was refluxed on a water bath, using 5 ml of THF as solvent, under a positive nitrogen atmosphere for 0.5 h. The reaction mixture was worked up by petroleum ether extractions followed by washings with D_2O. The petroleum ether solution was passed through a fine filter to get a clear solution which was then concentrated and dried. By repeating the process a couple of times, complete deuterium exchange, as determined by disappearance of ir absorption at 3310 cm (≡CH), was achieved to give 390 mg of **5e**: ir (CCl_4) 2590 (≡CD), 2125 (C≡C), 1690 cm^{-1} (C=O).

Naphthalene Sodium on Monodeuterated Acetylenic Ketone (5e). A solution of preformed naphthalene sodium in THF was added to a solution of 413 mg of monodeuterated acetylenic ketone **5e** in 5 ml of THF till a faint green end point. The color was allowed to discharge by itself after which the reaction mixture was worked up by extractions with petroleum ether (bp 40–60 °C) followed by D_2O washings. Petroleum ether was concentrated in vacuo and chromatographed over silica gel. Elution with pentane gave initially 240 mg of the reductively cyclized product. Later fractions gave 162 mg of 6α,6β-dimethyl-4,5-secocholest-3-yn-5ε-ol (**11**) which had ir (CCl_4) 3590 (OH), 3310 (≡CH), 2120 cm^{-1} (C≡C). The peak at 2590 cm^{-1} (≡CD) was completely absent. Its NMR was identical with that of undeuterated **11** showing that the 5α-H had not been replaced by deuterium.

The reductively cyclized product, on the other hand, contained considerable monodeuterated compound accompanying some undeuterated material. A careful comparison by NMR of the areas under the curve with the undeuterated **12** at the vinylic position indicated

that the singlet at δ 5.25 integrated for 0.8–1.0 protons and the relative areas at δ 5.25: 4.98 were 4:1.

4-Methyl-4,5-secocholest-3-yn-5-one (1c). 4-Methylcholest-4-en-3-one was prepared from cholestenone by treating with potassium *tert*-butoxide and methyl iodide in *tert*-butyl alcohol.[35] This was then epoxidized by addition of 30% H_2O_2 at a pH of about 12. The resulting 4,5-epoxy-4-methylcholestan-3-one was converted to **1c** as follows. To a solution of 1 g (2.5 mmol) of the above epoxy ketone in 250 ml of ethanol was added a solution of 470 mg of tosylhydrazine in 50 ml of ethanol. The reaction mixture was refluxed for 3–4 h. The alcohol was removed under vacuum and the resulting brown residue extracted with ether. The ether layer was washed with a solution of sodium bicarbonate, followed by water washings and dried over anhydrous sodium sulfate. Removal of ether gave a brown, gummy mass which was chromatographed over alumina. Elution with 1:1 hexane–benzene gave 650 mg of methyl acetylenic ketone **1c**. It was an oil and had $[\alpha]D$ +29° (c 0.12); ir (CCl_4) 2120 (C≡C), 1700 (C=O), 1460, 1365, 1265, 1070, 970, 940 cm^{-1}; NMR (CCl_4) δ 0.76 (3 H, s, C-18 methyl), 1.08 (3 H, s, C-19 methyl), 1.65 (3 H, s, $-C\equiv C-CH_3$). Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.02; H, 11.29.

Naphthalene Sodium on 4-Methyl-4,5-secocholest-3-yn-5-one (1c). A solution of 398 mg of 4-methyl-4,5-secocholest-3-yn-5-one in 5 ml of THF was titrated with naphthalene sodium in THF till a faint green color developed. The reaction mixture was worked up as usual, chromatographed on alumina, and eluted with pentane to remove all the naphthalene. Increasing the polarity by taking 10% benzene in pentane gave 220 mg of the unreacted starting material **1c** followed by 160 mg of the more polar mixture of stereoisomeric 3-ethylidene-*A*-norcholestan-5β-ols (**18a + 18b**). This mixture could not be separated and had $[\alpha]D$ +28 °C (c 0.13); ir (CCl_4) 3500 (OH), 1450, 1375, 1020, 978, 935, 912, 885 cm^{-1}. Anal. Calcd for $C_{28}H_{48}O$: C, 83.90; H, 12.07. Found: C, 83.56; H, 12.41.

Naphthalene Sodium/Methyl Iodide on 4-Methyl-4,5-secocholest-3-yn-5-one (1c). A solution of naphthalene sodium in DME was added to a well-stirred solution of 398 mg (1 mmol) of acetylenic ketone **1c** in 5 ml of DME till a faint green end point, and immediately 0.09 ml (1.3 mmol) of methyl iodide was added. The reaction mixture was stirred for the next 10 min, poured into water, neutralized, and ether extracted. The ether solution was then washed with a solution of sodium thiosulfate and finally with water. Removal of ether gave a gum which was chromatographed over silica gel and eluted with 1:1 hexane–benzene. Initial fractions gave 210 mg of 4,6α,6β-trimethyl-4,5-secocholest-3-yn-5-one (**5d**). It had $[\alpha]D$ −2° (c 0.14); ir (CCl_4) 2120 (C≡C), 1695 (C=O), 1580 cm^{-1}; NMR (CCl_4) δ 0.68 (3 H, s, C-18 methyl), 1.0, 1.15 (C-19 and C-6 methyls), 1.76 (3 H, s, $-C\equiv C-CH_3$). Anal. Calcd for $C_{30}H_{50}O$: C, 84.45; H, 11.81. Found: C, 84.19; H, 11.60.

Later fractions gave 160 mg of the cyclized compounds **18a** and **18b**.

Conversion of the Cyclized Tertiary Alcohols (18a and 18b) to Ketone (19). To a solution of 190 mg (0.5 mmol) of tertiary allylic alcohol (**18a** and **18b**) in 20 ml of acetone containing 2–3 drops of water was added a solution of 2 mg of *p*-toluenesulfonic acid in 2 ml of acetone with constant stirring under nitrogen atmosphere. After 1 h the reaction mixture was worked up and chromatographed over alumina. Elution with benzene gave initially an isomeric alcohol which had $[\alpha]D$ +55° (c 0.10). Later fractions gave the other isomeric alcohol which had $[\alpha]D$ +41° (c 0.11).

To a stirred solution of 1 ml of pyridine in CH_2Cl_2 was added 100 mg (1 mmol) of chromium trioxide. To this 100 mg (0.25 mmol) of the isomeric alcohol, $[\alpha]D$ +55°, in 5 ml of CH_2Cl_2 was added and left overnight. The reaction mixture was worked up as described elsewhere and chromatographed on alumina. Elution with benzene gave 60 mg of ketone **19**. It was crystallized from methanol–acetone and had mp 93–95 °C; $[\alpha]D$ +98° (c 0.12); uv λ_{max} (EtOH) 257 nm (ε 15 000); ir (CCl_4) 1700 (C=O), 1610 cm^{-1} (C=C); NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 1.01 (C-19 methyl), 2.04 (3 H, s, $-COCH_3$) shows no vinyl hydrogen. Anal. Calcd for $C_{28}H_{46}O{\cdot}CH_3OH$: C, 81.45; H, 11.08. Found: C, 81.58; H, 11.34.

Similar oxidation of the alcohol, $[\alpha]D$ +41°, gave the same ketone (**19**).

β-Epoxides of 18a and 18b. To 180 mg of the stereoisomeric allylic alcohols (**18a** and **18b**) was added 8 ml of 0.77 N perbenzoic acid in chloroform and the mixture was left overnight at 5 °C. It was worked up as described earlier and chromatographed over alumina. Elution with benzene gave initially 68 mg of **21** which crystallized readily from methanol. It had mp 108–110 °C; $[\alpha]D$ +11° (c 0.11); ir (KBr) 3400, 2880, 1450, 1370, 1025 cm^{-1}; NMR (CCl_4) δ 0.71 (3 H, s, C-18 methyl), 0.97 (C-19 methyl), 1.5 (3 H, d, J = 6 Hz), and 3.11 (1 H, q, J = 6 Hz)[$-CH(O)CH_3$]. Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.47; H, 11.35.

Later fractions gave 92 mg of **20** which was crystallized from methanol. It had mp 96–98 °C $[\alpha]D$ +10° (c 0.13); ir (KBr) 3390, 2880, 1450, 1370, 1025 cm^{-1}; NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 1.01 (3 H, s, C-19 methyl), 1.28 (3 H, d, J = 6 Hz), and 3.11 (1 H, q, J = 6 Hz) [$-CH(O)CH_3$]. Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.79; H, 11.39.

3α-Ethyl-*A*-norcholestane-3β,5β-diol (22). To a solution of 104 mg (0.25 mmol) of the epoxy tertiary alcohol **20** in 50 ml of dry ether was added 400 mg of $LiAlH_4$ and the mixture was refluxed for 3 h. After the addition of aqueous sodium potassium tartrate, the product was extracted with ether, dried, and concentrated under vacuum to yield a residue which was chromatographed over alumina. Elution with 1:1 benzene–ether gave 80 mg of the diol **22**. On crystallization from methanol, it had mp 113–114 °C; $[\alpha]D$ −6° (c 0.13); ir (KBr) 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.65 (3 H, s, C-18 methyl) and 1.0 (C-19 methyl). [The corresponding 3α-methyl-*A*-norcholestane-3β,5β-diol has NMR ($CDCl_3$) δ 0.65 (C-18 methyl) and 1.00 (C-19 methyl)].[2] Anal. Calcd for $C_{28}H_{50}O_2$: C, 80.32; H, 12.03. Found: C, 80.15; H, 11.87.

Reduction of **21** under the above conditions gave the same diol **22** as confirmed by identity of melting point, $[\alpha]D$, ir, and NMR.

4-Methyl-4,5-secocholest-3-yn-5α- and -5β-ols and 5-Ketal (24) from 1c. To a solution of 396 mg (1 mmol) of methyl acetylenic ketone **1c** in 20 ml of methanol was added 111 mg (3 mmol) of sodium borohydride in one portion. The reaction mixture was worked up as described earlier and chromatographed over alumina. Elution with 1:1 hexane–benzene gave 160 mg of 4-methyl-4,5-secocholest-3-yn-5α-ol. It had mp 87–88 °C; $[\alpha]D$ +32°.

Later elutions gave 210 mg of 4-methyl-4,5-secocholest-3-yn-5β-ol (**23**). It had mp 78–80 °C; $[\alpha]D$ +12° (c 0.12). (The configurations of these compounds have been tentatively assigned on the basis of their rotations.)

To a solution of 990 mg (2.5 mmol) of **1c** in 50 ml of dry benzene was added 50 mg of *p*-toluenesulfonic acid and 248 mg (4 mmol) of ethylene glycol. The flask was attached to a Dean-Stark unit and water was azeotroped out. Workup and chromatography gave 740 mg of 4-methyl-4,5-secocholest-3-yne-5-ketal (**24**).

Naphthalene Sodium on 23 and 24. A solution of naphthalene sodium in THF was added to a solution of 398 mg (1 mmol) of **23** in 5 ml of THF till a faint green end point. By estimation, it was found that 1.0 mmol of the reagent was consumed. Workup and chromatography as in earlier experiments gave 388 mg of starting material **23**.

Addition of 3 mmol of the reagent to 398 mg (1 mmol) of **23** and stirring for 25 min gave after workup and chromatography 390 mg of the starting material **23**.

A solution of naphthalene sodium in THF was added to a solution of 104 mg (0.25 mmol) of the ketal **24** in 3 ml of THF till a faint green end point. It took up 0.1 mmol of the reagent. Workup and chromatography gave 100 mg of the starting material **24**. Repetition of the above experiment with 104 mg (0.25 mmol) of **24** by adding 0.5 mmol of the reagent and stirring for 25 min gave, after workup and chromatography, 101 mg of the starting ketal **24**.

4a,5-Seco-*A*-homocholest-4(4a)-yn-5-one (25). Sodamide[14] was prepared by bubbling ammonia into a solution of 0.6 N naphthalene sodium externally cooled in an ice bath till the color changed from green to greyish. This solution was practically free of sodium. Ammonia was then displaced by nitrogen and the resulting turbid solution was added in fivefold excess to a solution of 196 mg of methyl acetylenic ketone **1c** in 30 ml of dry toluene. The mixture was refluxed for 12 h and allowed to cool to room temperature. Aqueous HCl was added slowly to make it acidic and then the mixture was stirred for 20 min. The two layers were separated and the aqueous layer was saturated with brine solution and extracted with ether. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Removal of solvent and chromatography over alumina gave, after naphthalene, 280 mg of an oily mixture which was not identified.

Later elutions gave 30 mg of the isomerized acetylenic ketone **25** as shown by ir and by formation of Ag salt. Its constants are given below.

To obtain better yields of the isomerized ketone **25**, the above experiment was repeated with the ketal **24**. Sodamide prepared as described in the previous reaction was added in excess in a solution of 600 mg (1.4 mmol) of ketal **24** in 80 ml of dry toluene and refluxed for 12 h. Workup and chromatography as before gave 400 mg of the isomerized ketal. This ketal was dissolved in 5 ml of THF, treated with 10 ml of 10% H_2SO_4, and left overnight. Workup and chromatography gave 300 mg of 4a,5-seco-*A*-homocholest-4(4a)-yn-5-one (**25**) as an oil: ir (CCl_4) 3310 (≡CH), 2210 (C≡C), 1709 cm^{-1} (C=O); NMR (CCl_4) δ 0.75 (3 H, s, C-18 methyl), 1.08 (C-19 methyl). Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.10; H, 11.29.

4-Methylenecholestan-5β-ol (26). A solution of preformed naphthalene sodium in THF was added to a stirred solution of 198 mg (0.5 mmol) of the acetylenic ketone **25** in 3 ml of THF to a faint green end point. Approximately 2 mmol of the reagent was consumed per millimole of the starting material. Workup and chromatography over alumina and eluting with pentane gave 20 mg of the unreacted starting material **25.** Increasing the polarity of the eluent gave 160 mg of 4-methylenecholestan-5β-ol (**26**). It had $[\alpha]_D$ +21° (*c* 0.11) but could not be crystallized: ir (CCl_4) 3510 (OH), 910 cm^{-1} (=CH_2); NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 1.03 (C-19 methyl), 4.96 (2 H, m, =CH_2).

4α-Methylcholestane-4β,5β-diol (30) from 4-Methylcholest-3-en-5β-ol (28). To 100 mg (0.25 mmol) of the allylic alcohol **28**[15] was added 4 ml of 0.77 N perbenzoic acid in chloroform and the mixture was left overnight at 5 °C. Workup and crystallization from methanol gave 72 mg of the epoxide **29.** It had mp 113–114 °C; $[\alpha]_D$ +46° (*c* 0.13); ir (KBr) 3340 (OH), 1030 cm^{-1}; NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 0.97 (C-19 methyl), 1.38 (3 H, s, C-4 methyl), 3.18 (1 H, broad s, C-3 H). Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.30; H, 11.70.

To a solution of 104 mg (0.25 mmol) of the epoxy alcohol **29** in 50 ml of dry ether was added 400 mg of $LiAlH_4$ and the mixture was refluxed for 3 hr. Workup and crystallization from methanol gave 70 mg of 4α-methylcholestane-4β,5β-diol (**30**). It had mp 163–164 °C; $[\alpha]_D$ +8° (c 0.11); ir (KBr) 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.65 (3 H, s, C-18 methyl), 0.98 (3 H, s, C-19 methyl), 1.45 (3 H, s, C-4 methyl). Anal. Calcd for $C_{28}H_{50}O_2$: C, 80.32; H, 12.03. Found: C, 80.18; H, 11.67.

The same diol **30** was produced along with an isomer by treating 300 mg of 4-methylcholest-4-ene[3] (obtained by $LiAlH_4/AlCl_3$ reduction of 4-methylcholest-4-en-3-one) dissolved in 25 ml of ether with a solution of 300 mg of OsO_4 in 2.5 ml of pyridine and working up after 40 h.

Conversion of 26 via Epoxide 27 to Diol 30. To 100 mg (0.25 mmol) of the tertiary allylic alcohol **26** was added 4 ml of 0.77 N perbenzoic acid in chloroform and the mixture was left overnight at 5 °C. Workup and crystallization from aqueous methanol gave 72 mg of the corresponding epoxide **27.** It had mp 110–112 °C; $[\alpha]_D$ +7° (*c* 0.12); ir (KBr) 3350 cm^{-1} (OH); NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 1.0 (C-19 methyl), 2.69 (1 H, d, J = 5 Hz), and 3.12 (1 H, d of d, J = 5 and 1.5 Hz) [–(O)CH_2]. Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.57; H, 11.72.

To a solution of 104 mg (0.25 mmol) of the above epoxy tertiary alcohol **27** in 50 ml of dry ether was added 400 mg of $LiAlH_4$ and the mixture was refluxed for 3 h. Workup of the reaction mixture followed by crystallization from methanol gave 70 mg of **30** identical in its melting point, $[\alpha]_D$, ir, and NMR with that prepared in the previous experiment.

O-Methylation of Cholesterol with Methyl Iodide and Naphthalene Sodium. A solution of naphthalene sodium in DME was added to a stirred solution of 386 mg (1 mmol) of cholesterol in 5 ml of DME to a faint green end point, followed by the immediate addition of 0.08 ml (1.3 mmol) of methyl iodide in 3 ml of DME. The reaction mixture was worked up as usual and chromatographed on silica gel. Elution with pentane followed by more polar mixtures with benzene gave after naphthalene 330 mg of 3β-methoxycholest-5-ene. It had mp 78 °C (lit.[36] mp 84 °C); NMR (CCl_4) δ 0.71 (3 H, s, C-18 methyl), 1.06 (3 H, s, C-19 methyl), 3.20 (1 H, m, C-3 H), 3.26 (3 H, s, –OCH_3), 5.26 (1 H, m, C-6 H).

The methylation was carried out both in THF and in DME. The proportion of the methyl ether formed varied with solvent as well as the concentration of the reagent.

Similar methylations using naphthalene lithium and naphthalene potassium were also carried out. The results are given in Table II.

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Appendix

Additional evidence which strongly supports the mechanism given in Schemes V and VI has now been obtained. Reverse dropwise addition of **1c** in THF to naphthalene sodium in THF gave a 70 (±3):30(±3) ratio of **18a:18b.** This means that initial addition across the acetylene is syn and the corresponding vinyl radical is trapped by reduction to vinyl carbanion before it equilibrates to the extent that it does in normal addition. This is to be expected because of the excess of reducing agent present during the reverse addition. This dependency of ratio **18a:18b** on mode of addition would not be expected if there was equilibration at the vinyl carbanion stage. This possibility had been considered unlikely because of the results of vinyl halide reductions with naphthalene sodium.[32]

It also became essential to put the configurational assignment of **18a** and **18b** on a stronger footing. This has been done using 360-MHz NMR.[33] Decoupling with the vinyl hydrogen showed that the methyl of the ethylidene group of the major isomer occurs at δ 1.60 and has a distinctly smaller band-width at half height than the methyl at δ 1.75 due to the minor isomer. In the structure **18b** assigned to the latter, the methylene at C-2 is trans to the methyl and hence greater homoallylic coupling[34] is to be expected.

Registry No.—**1a,** 21489-86-1; **1b,** 17541-44-5; **1c,** 58502-98-0; **2c,** 58502-99-1; **5a,** 58503-00-7; **5c,** 52091-54-0; **5d,** 58503-01-8; **5e,** 58503-02-9; **6,** 52091-60-8; **7a,** 58503-03-0; **11,** 58503-04-1; **11** acetate, 58512-16-6; **12,** 58503-05-2; **13,** 58503-06-3; **14,** 58503-07-4; **15,** 58503-08-5; **16,** 58503-09-6; **17,** 58503-10-9; **18a,** 58503-11-0; **18b,** 58503-12-1; **19,** 24298-82-6; **20,** 58503-13-2; **21,** 58503-14-3; **22,** 58503-15-4; **23,** 58503-16-5; **23** 5α analogue, 58526-09-3; **24,** 58503-17-6; **25,** 58503-18-7; **26,** 58503-19-8; **27,** 58503-20-1; **28,** 58503-21-2; **29,** 58503-22-3; **30,** 58503-23-4; naphthalene sodium, 3481-12-7; naphthalene potassium, 4216-48-2; naphthalene lithium, 7308-67-0; 4,5-epoxy-4-methylcholestan-3-one, 58526-10-6; tosylhydrazine, 539-44-6; cholesterol, 57-88-7; methyl iodide, 74-88-4; 3β-methoxycholest-5-ene, 1174-92-1.

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Nucleophilic Additions to Aldehydes and Ketones. 2.[1] Reactions of Heterocyclic Aldehydes with Hydroxide Ions

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Three groups of heterocyclic carboxaldehydes can be distinguished according to their reactivity toward hydroxide ions: to the first group belong nonhydrated five-membered heterocyclic aldehydes (derivatives of furan, thiophene, and N-substituted pyrrole) which add hydroxide ions to the carbon–oxygen double bond in a similar way as benzaldehydes. The second groups consists of pyrrole and indole derivatives where in alkaline media the NH group dissociates before the formyl group is attacked. Hydrated aldehydes (pyridine, thiazole, and imidazole derivatives) belonging to the third group show dissociation of the geminal diol. Equilibrium constants of these three types of reactions were measured spectrophotometrically. Most of the aldehydes studied undergo electrooxidation as geminal diol anions which was followed polarographically. Ring substituents and the nature of the heteroatom affect the values of equilibrium constants and half-wave potentials. In indole and pyrrole derivatives a specific interaction between the formyl group and the heterocycle is indicated.

In previous work[5] an acidity scale J_- has been developed to be used in strongly alkaline media for reactions involving addition of hydroxide ions. Some meta- and para-substituted benzaldehydes have been used as indicators for characterizing acidity of aqueous sodium hydroxide solutions. By means of this scale thermodynamic equilibrium constants for hydroxide ion additions to other meta- and para-substituted benzaldehydes were determined.[1] Corresponding pK values were correlated with Hammett substituent constants σ by means of a reaction constant $\rho = 2.76$ [$r = 0.994$, S (est) 0.012]. Later Greenzaid[6] also measured spectrophotometrically the ratio of concentrations of the anion of the geminal diol to that of the free aldehydic form. The concentration of an unspecified hydroxide was used in calculation of equilibrium constants of the reaction 1

$$\mathrm{ArCHO} + \mathrm{OH^-} \overset{K}{\rightleftharpoons} \mathrm{ArCH(OH)O^-} \qquad (1)$$

instead of acidity functions and the activity term $y_{\mathrm{ArCH(O^-)OH}}/y_{\mathrm{ArCHO}}y_{\mathrm{OH^-}}$ was neglected. This approach restricted the study to solutions of the unspecified base below 1.5 M and this in turn limited the investigation to compounds with electronegative substituents. Reported values could have been considered as practical equilibrium constants, provided that ionic strength was kept constant. As this was not the case, the values reported by Greenzaid[6] correspond for each compound to another ionic strength and hence can be considered only as "crude practical constants". Correlation of these approximate values for the limited group of monosubstituted and some disubstituted benzaldehydes accessible to measurement with Hammett substituent constants σ greater than zero, gave $\rho = 2.24$ ($r = 0.982$). The susceptibility of benzaldehydes to substituent effects for hydroxide addition is similar to that for methoxide addition, reported recently.[7]

The anion of the geminal diol has been proved[8] to be the electroactive form in the electrooxidation of benzaldehydes in alkaline media. Rate constants for the addition of the hydroxide ion and the reverse reaction obtained from polarographic data on benzaldehyde oxidations were about 1.5 orders of magnitude larger than values for 3- and 4-chlorobenzaldehydes measured by stopped-flow technique.[9] This difference might reflect different reaction conditions used, but also may be caused by the effect of the electric field in the vicinity of the electrode. Another electrochemical method, based on constant potential electrolysis of the corresponding aromatic acid at a rotating disc electrode at pH 6.2, was proposed.[10] The rate constants found[10] for 3-chlorobenzaldehyde which are seven to eight orders of magnitude smaller than those above were attributed to loss of water rather than OH^-. Since pH dependence of these constants has not been studied, it is not possible to comment on their attribution, but the value of the equilibrium constant, indicating that about 50% of 3-chlorobenzaldehyde exists in hydrated form, is clearly doubtful.

In this contribution both the studies of the equilibria involving addition of hydroxide and the electrooxidation of the aldehydic group are extended to heterocyclic compounds bearing an aldehydic group. Attention is being paid to the role of the nature of the heterocyclic ring and effect of substituents as well as to competitive reactions.

Experimental Section

Chemicals and Solutions. Fural, 5-methylfural, 5-hydroxymethylfural, 2-thiophenecarboxaldehyde, 3-methyl-2-thiophenecarboxaldehyde, 5-bromo-2-thiophenecarboxaldehyde, 2-pyrrolecarboxaldehyde, *N*-methyl-2-pyrrolecarboxaldehyde, 3-indolecarboxaldehyde, *N*-benzyl-3-indolecarboxaldehyde, *N*-ethyl-3-carbazolecarboxaldehyde, and 3-cinnolinecarboxaldehyde (Aldrich Chemical Co.), *N*-phenyl-2,5-dimethyl-3-pyrrolecarboxaldehyde

Table I. Oxidation Half-Wave Potentials and Equilibrium Constants of Addition of Hydroxide Ions to Nonhydrated Heterocyclic Aldehydes

Registry no.	Aldehyde	λ_{max}, nm	$\epsilon \times 10^{-3}$, l. mol^{-1} cm^{-1}	pK'[a]	λ_{meas},[b] nm	Δ[c]	$E_{1/2}$,[d] V vs. SCE: 5.0 M NaOH	$E_{1/2}$,[d] V vs. SCE: 1.0 M NaOH
98-01-1	Fural	278	13.6	14.75	277	−1.09	−0.36	−0.24
620-02-0	5-Methylfural	293	15.8	15.65	293	−1.40	−0.37[e]	−0.22
698-63-5	5-Nitrofural	227	6.8	11.82	290	−1.08	−0.37	
		310	11.0					
67-47-0	5-Hydroxymethylfural	230	2.0	*f*	*f*	*f*	*f*	*f*
		280	14.8					
98-03-3	2-Thiophenecarboxaldehyde	264	23.0	15.21	290	−1.01	−0.45[e]	−0.30
		292	16.0					
4701-17-1	5-Bromo-2-thiophenecarboxaldehyde	270	5.0	14.64	302	−0.98	−0.47	−0.39
		302	12.0					
5834-16-2	3-Methyl-2-thiophenecarboxaldehyde	280	13.0	15.75	282	−1.08	−0.34	−0.22
1192-58-1	1-Methyl-2-pyrrolecarboxaldehyde	255	2.0	≈17.5	293	*g*	−0.23	−0.20
		293	16.0					
83-18-1	1-Phenyl-2,5-dimethyl-3-pyrrolecarboxaldehyde	260	8.5	≈16.0	260	*g*	*h*	*h*
		303	5.0					
7570-45-8	*N*-Ethyl-3-carbazolecarboxaldehyde	233	21.0	13.95	233	−0.94	−0.22	−0.14
		242	18.0		276			
		276	24.0		293			
		293	18.0					
		335[i]	10.0					
58503-24-5	*N*-Ethyl-3-carbazolecarboxaldehyde geminal diol anion	248	≈ 4.0	*j*	*j*	*j*	−0.22	−0.14
		275	≈ 4.0					
		300	12.0					
		350	10.0					
10511-51-0	*N*-Benzyl-3-indolecarboxaldehyde	248	7.0	*j*	*j*	*j*	*j*	*j*
		263	≈ 4.0					
		305	8.0					

[a] pK' = pK + pK_w; K = [ArCH(OH)O$^-$]/[ArCHO][OH$^-$]. [b] Wavelength at which the absorbance was measured for calculation of K. [c] Δ = slope of the plot of log[ArCHO]/[ArCH(OH)O$^-$] vs. acidity function J_-. [d] Polarographic half-wave potential of the anodic oxidation wave. [e] Polarographic curve shows a maximum. [f] Fast competitive homogeneous chemical reaction in alkaline media prevented measurement. [g] Only part of dissociation curve experimentally accessible. [h] No anodic wave observed before potential of mercury dissolution. [i] Wide band. [j] Reacts in alkaline media, but does not add OH$^-$ to CHO.

(Eastman Kodak), 5-nitrofural (Pfalz and Bauer), 2-indolecarboxaldehyde, and 1-methyl-2-imidazolecarboxaldehyde (kindly donated by Professor F. Popp, Clarkson College of Technology, Potsdam, N.Y.), 2-imidazolecarboxaldehyde, 2-thiazolecarboxaldehyde, and 2-benzothiazolecarboxaldehyde (kindly donated by Professor H. Lund, Aarhus University, Denmark) were freshly distilled, recrystallized, or sublimated. Purity was checked by gas–liquid chromatography. Stock solutions (0.01 M) of these aldehydes were prepared freshly in 96% ethanol.

Sodium hydroxide solutions were prepared from 0.1 and 1.0 M Baker reagent grade Dilut-it standardized solutions and from 50% Baker Analyzed sodium hydroxide containing less than 0.03% carbonate, shown to be 18.86 M by standardization with potassium acid phthalate. These standards, kept carbonate free, were diluted under nitrogen with distilled freshly boiled water cooled in a nitrogen stream.

All buffers used for pH < 12 were prepared from reagent grade chemicals.

Apparatus. Electronic spectra were recorded by means of a Unicam SP-800A recording spectrophotometer (Pye-Unicam, Cambridge, England). Cells (10 mm) were placed in a thermostated compartment and temperature maintained at 25 ± 0.01 °C.

Polarographic current–voltage curves (dc) were obtained with a Model 174 polarographic analyzer (Princeton Applied Research, Princeton, N.J.) in connection with a Hewlett-Packard 7004B X-Y recorder. The capillary used had in 1 M potassium chloride at 0.0 V (SCE) the following characteristics: rate of flow m = 1.9 mg/s, drop time t_1 = 3.4 s at h = 65 cm.

A modified Kalousek cell was used with a spectroscopic grade carbon rod immersed in 5 M sodium hydroxide as a separated reference cathode.[11] To minimize the effect of polarization of the reference cathode, the current–voltage curves were recorded from negative to positive potentials.

pH measurements were carried out with a Sargent-Welch Model NX pH meter with a Sargent S-30072-15 combination glass electrode as well as with a Radiometer electrode G-202B for measurements in alkaline region.

Procedures. For recording of the uv spectra an aliquot of the stock solution was added to an aqueous solution of a buffer or of sodium hydroxide so that the final aqueous solution contained 1 × 10^{-4} M aldehyde and 1% ethanol.

For each aldehyde spectra were recorded in buffers of varying pH or in sodium hydroxide solutions of varying concentration. For each aldehyde 10–15 spectra were recorded in solutions chosen so as to straddle the pK value. Spectra were always recorded within 2 min after mixing the solutions and then again after 5 min to check for any changes with time.

Polarographic anodic waves were recorded in 5 and 1 M sodium hydroxide solutions containing 2 × 10^{-4} M aldehyde and 2% ethanol. Solutions for polarographic electrolysis were freshly prepared from stock solutions and the curves were checked for any changes with time.

Evaluation of Equilibrium Constants. To evaluate the equilibrium constant K corresponding to reaction 1 in most cases the decrease of the absorbance of the free carbonyl form was followed. The values of wavelengths used are given for individual compounds in Tables I–III. In some cases the geminal diol anion has shown an absorbance (corresponding to aromatic system deprived of the conjugation with the carbonyl group) the increase of which was followed (cf. Table I–III). The ratio [ArCH(OH)O$^-$]/[ArCHO] was found at a given wavelength from $(A_0 - A)/(A - A_r)$ where A_0 is the absorbance due to pure carbonyl form (measured at sufficiently low sodium hydroxide concentration or in a buffer of sufficiently low pH), A_r absorbance of the pure geminal diol anion ArCH(OH)O$^-$ (measured at so high pH or sodium hydroxide concentration that conversion can be regarded as complete), and A absorbance of the solution in the acidity range between the two extremes.

The value of log ([ArCH(OH)O$^-$]/[ArCHO]) was then plotted against pH or J_- function.[5] For all aldehydes studied this plot was found linear with a slope (Δ) given in Tables I and III. The value of

Table II. Oxidation Half-Wave Potentials and Dissociation Constants of Heterocyclic Aldehydes Bearing on NH Group

Registry no.	Aldehyde	λ_{max}, nm	$\epsilon \times 10^{-3}$, l. mol^{-1} cm^{-1}	pK_N[a]	λ^N_{meas},[b] nm	pK'[c]	λ_{meas},[d] nm	$E_{1/2}$,[e] V vs. SCE 5 M NaOH	$E_{1/2}$,[e] V vs. SCE 1 M NaOH
1003-29-8	2-Pyrrolecarboxaldehyde	250 293	≈ 3.0 16.0	13.65	293 315	>17		−0.22	−0.18
58503-25-6	2-Pyrrolecarboxaldehyde iminate anion	265 315	≈ 1.0 22.0					−0.22	−0.18
19005-93-7	2-Indolecarboxaldehyde	235 310	13.0 23.0	14.00	310 335	>17[f]		−0.40	−0.29
58503-26-7	2-Indolecarboxaldehyde iminate anion	247 335	18.0 24.0					−0.40	−0.29
487-89-8	3-Indolecarboxaldehyde	244 261 300	13.0 13.0 14.0	12.33 12.36[g]	324	>16		*h*	*h*
58503-27-8	3-Indolecarboxaldehyde iminate anion	265 324	22.0 22.0					*h*	*h*
10111-08-7	2-Imidazolecarboxaldehyde	215 287	4.0 5.0	10.08[i] 10.34[i]	285 315		310	−0.21	−0.18
58503-28-9	2-Imidazolecarboxaldehyde iminate anion	310	8.0			≈13.5[i]			

[a] $K_N = [HetN^-][H^+]/[HetNH]$. [b] Wavelength at which the absorbance was measured for calculation of K_N. [c] $pK' = pK + pK_w$; $K = [ArCH(OH)O^-]/[ArCHO][OH^-]$. [d] Wavelength at which absorbance was measured for calculation of K_{CHO}. [e] Polarographic half-wave potential of the anodic oxidation wave. [f] In 4 M NaOH change of the solution and development of yellow coloration observed, but no time change found in 10 M NaOH. [g] Reference 10. [h] No anodic wave observed before potential of mercury dissolution. [i] Overall equilibrium constants, aldehydic group is present in equilibrium at least 70% in hydrated form.

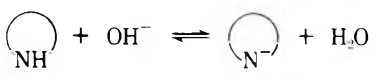
Table III. Oxidation Half-Wave Potentials and Dissociation Constants of the Geminal Diol Group of Some Hydrated Heterocyclic Aldehydes

Registry no.	Aldehyde	λ_{max}, nm	$\epsilon \times 10^{-3}$, l. mol^{-1} cm^{-1}	pK_s[a]	λ_{meas}[b]	Δ[c]	$E_{1/2}$,[d] V vs. SCE 5 M NaOH	$E_{1/2}$,[d] V vs. SCE 1 M NaOH
10200-59-6	2-Thiazolecarboxaldehyde	237 295	0.3 0.4	11.2[e]	295	−1.00	−0.38	−0.31
6639-57-2	2-Benzothiazolecarboxaldehyde	217 255 296	18.0 7.0 2.0	10.7[f]	315	−1.30	−0.55	−0.48
51073-57-5	3-Cinnolinecarboxaldehyde	229 250 285 325	36.0 18.0 3.0 4.0	11.95[g]	250	−1.00	−0.38	−0.33
	2-Imidazolecarboxaldehyde iminate anion	310	8.0	≈13.5[i]	310	−0.98	−0.21	−0.18
13750-81-7	*N*-Methyl-2-imidazolecarboxaldehyde	223 289	0.4 1.3	13.50[j]	289	−1.20	−0.23	−0.14

[a] Overall equilibrium constant, $K_s = [ArCH(OH)O^-][H^+]/([ArCHO] + (ArCH(OH)_2])$. [b] Wavelength at which the absorbance was measured for calculation of K_s. [c] Δ = slope of the plot of $\log[ArCHO]/[ArCH(OH)O^-]$ vs. acidity function J_-. [d] Polarographic half-wave potential of the anodic oxidation wave. [e] About 80% hydrated form. [f] About 90% hydrated. [g] Strong hydration. [h] See also Table II. [i] At least 70% hydrated form. [j] Weak hydration.

pH or J_- where $\log([ArCH(OH)O^-]/[ArCHO])$ was equal to zero was considered equal to pK.

A completely analogous procedure was applied to determination of values pK_N corresponding to equilibrium 2:



(2)

In most cases both the decrease of the absorbance of the parent compound and the increase of the absorbance of the iminate ion (often stronger) was followed at wavelengths given in Table II.

Half-Wave Potentials. Measurements of half-wave potentials were made relative to that of the unsubstituted benzaldehyde as an internal standard the waves of which were recorded prior to and after recording of each series of waves. Values of half-wave potentials of benzaldehyde were taken[13] as −0.29 V in 1 M sodium hydroxide and as −0.44 V in 5 M sodium hydroxide, both expressed against SCE. Examples of polarographic curves are given in Figure 1.

Results and Discussion

Classification of Systems. Heterocyclic aldehydes studies can be divided into three groups: to the first two groups belong five-membered "neutral" aldehydes with an excess of π electrons;[12] to the third five- and six-membered "basic" aldehydes with a π-electron deficiency.

Formyl groups of aldehydes belonging to the first two groups show little hydration at lower pH values, in a way as most of the substituted benzaldehydes.[13] Values of molar absorptivities and their independence of solvent (when aqueous, DMF and Me_2SO solutions were compared) as well

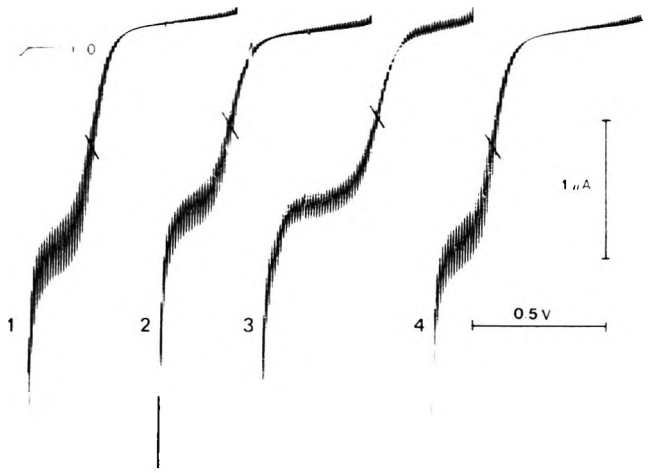


Figure 1. Anodic waves of heterocyclic aldehydes. 1 M sodium hydroxide, 2×10^{-4} M aldehyde, 2% ethanol. Compounds (half-wave potentials vs. SCE): (1) 2-thiophenecarboxaldehyde (−0.30 V); (2) 2-thiazolecarboxaldehyde (−0.31 V); (3) 2-benzthiazolecarboxaldehyde (−0.48 V); (4) benzaldehyde (−0.29 V). Curves recorded from −0.75 V (vs. Carbon rod in 5 M sodium hydroxide) to positive potentials, rate of scanning 200 mV/min.

as the height of polarographic reduction and oxidation waves indicate that less than 10% of these compounds in neutral or slightly acidic media exists in the geminal diol ($ArCH(OH)_2$) form.

The division of the first two groups is based on the nature of their acid–base properties. To the first group are assigned aldehydes which in strongly alkaline media add a hydroxide ion to the aldehydic group according to reaction 1, in a similar way as benzaldehydes.[5] Derivatives of furan and thiophene belong to this group as well as those derivatives of pyrrole which bear an alkyl or aryl group on the heterocyclic nitrogen.

To the second group belong such heterocyclic aldehydes where the attack of hydroxide ion in alkaline solution occurs preferentially on the heterocycle and results in the dissociation of the N–H bond. This group is represented by pyrrole and indole derivatives with an unsubstituted NH group. These compounds show thus the same type of acid–base properties as other indole and pyrrole derivatives.[14]

To the third group belong thiazole, imidazole, and pyridine derivatives which exist in aqueous solutions in an equilibrium in which a considerable fraction of the aldehyde is present in the hydrated form.

Differentiation between CHO and NH Reactions. Distinction between the type of reaction in these two groups of carboxaldehydes is possible on the basis of their spectral behavior: compounds belonging to the first group show with increasing hydroxide concentration a decrease of the absorption band in the 250–300-nm region as corresponds to the shift of equilibrium 1 in favor of the geminal diol anion. Reaction of the compounds belonging to the second group with bases yielding iminate anions—pyrrolate or indolate—is manifested by an appearance of a new absorption band at longer wavelength and with greater molar absorptivity than shown by the neutral molecule.

The change in spectra observed for systems involving formation of a geminal diol anion is due to an annihilation of conjugation between the aromatic ring and the carbonyl group. The resulting adduct—the geminal diol anion—is either practically transparent in the 250–300-nm range or shows a considerably weaker absorption band due to the transition involving only the π electrons of the aromatic ring.

The shift toward longer wavelength when compared with the conjugate acid and the increase in absorptivity accompanying the formation of the iminate ion resembles behavior of carbanions and carbanion enolates, where the effect is usually interpreted as due to the participation of the electrons of the unit charge in the conjugated system. Nevertheless, we have recently shown[15] that electronic spectra can be observed for anions containing only σ bonds and indicated that such spectra might involve photolysis and formation of hydrated electrons. Attempts are being made to prove or exclude such a possibility for iminate ions.

An alternative possibility for differentiation of proton abstraction from hydroxide ion addition would be to distinguish whether the dependence of the value of ratio of the concentrations of the conjugate acid and base fits better the H_- or the J_- acidity scales.[5,16] Nevertheless, significant differences between the two scales are observed at so high sodium hydroxide concentrations that this diagnostic tool cannot be practically applied to the study of most of the presently studied systems.

Evaluation. Equilibrium constants for reactions of nonhydrated aldehydes resulting in addition of the hydroxide ion are summarized in Table I, those for aldehydes where dissociation of the NH group occurs first in Table II. Half-wave potentials of anodic waves are also included.

For all compounds reported in Table I a decrease of the ArCO absorption band was observed, indicating addition of OH^- ions with the exception of *N*-benzyl-3-indolecarboxaldehyde, which undergoes a different reaction. Formation of a new band at longer wavelengths (at 315 nm) indicated the possibility of carbanion formation. For all aldehydes, where measurement of the ratio $[ArCH(OH)O^-]/[ArCHO]$ was possible over a sufficiently wide range of sodium hydroxide concentration, the plot of log $[ArCH(OH)O^-]/[ArCHO]$ as a function of J_- values was found linear. This allows the conclusion that all these aldehydes add hydroxide ion in a simple reversible reaction, as has been proved for substituted benzaldehydes.[5,13] Consecutive or competitive reactions like the Cannizzaro reaction or ring opening do not affect values in Table I. The slope of the aforementioned linear plot (Δ) varies for the majority of compounds studied between −0.94 and −1.09 (Table I) indicating that the application of the J_- acidity scale for these compounds is permissible. Deviations in the value of Δ (Table I) observed for methyl-substituted compounds (5-methylfural and 3-methyl-2-thiophenecarboxaldehyde) might be due to steric effects, but further data on larger alkyl groups and dependence on position would be needed before they can be discussed in more detail. Reversibility of the reaction has been proved in all instances by recovery of the aldehyde after acidification.

In addition to the rapidly established equilibrium corresponding to reaction 1, all furan derivatives have shown a considerably slower, consecutive reaction, fastest for 5-hydroxymethylfural. The nature of this process, considered to be a Cannizzaro or ring opening reaction, is under investigation.

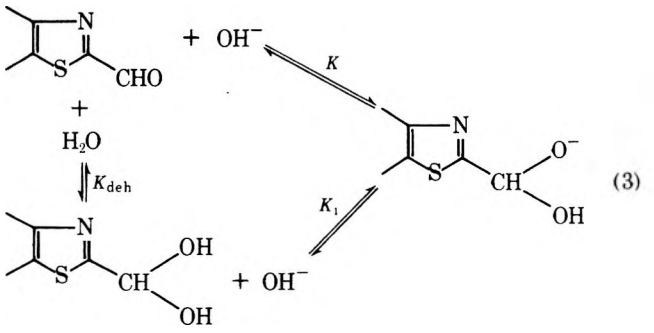
Study of dissociation following reaction 2 (Table II) presented no complications, with the exception of the 2-imidazolecarboxaldehyde, which was present in the aqueous solutions also in hydrated form and will be discussed in the next section. Where comparison with literature was possible (i.e., for 3-indolecarboxaldehyde) agreement of our and reported[14] data was good.

Anodic waves of aldehydes which form the electroactive[8] geminal diol anion (Table I) correspond to oxidation of the aldehyde with formation of the corresponding carboxylic acid. Electrolysis products of the iminates (Table II) were not identified and the process involved is further studied.

Hydrated Aldehydes. Aldehydes derived from "basic" or π-deficient heterocyclic rings are strongly hydrated. The most typical representatives of this group, pyridinecarboxaldehydes, have been studied in sufficient detail[17–19] and were

not thus included in this investigation. Quinolinecarboxaldehydes[17] are more strongly hydrated both in the protonated and uncharged form than the corresponding pyridinecarboxaldehydes. For thiazole- and imidazolecarboxaldehydes information about the position of the hydration–dehydration equilibria is rather scarce. 5-Imidazolecarboxaldehyde is estimated[20] to be about 50% hydrated in the protonated form and less in the uncharged form. 2-Imidazolecarboxaldehyde[21,22] and its *N*-alkyl derivatives[22] are more strongly hydrated than the 5 isomer. For 2-thiazolecarboxaldehyde stronger hydration of the cationic form than that of the free molecule is observed,[17] both being stronger than that for 5-imidazolecarboxaldehyde. Estimates from our spectral data (Table III) indicate that for the unprotonated forms of 2-thiazole, 2-benzothioazole, and 2-imidazole 70–90% of the aldehyde is in equilibrium present in hydrated form, whereas 1-methyl-2-imidazolecarboxaldehyde is only slightly, if at all, hydrated.

The reported value of pK_s (Table III) has different physical meaning for thiazole and imidazole derivatives. For thiazolecarboxaldehydes the overall acid–base reaction involves only the aldehydic group and eq 3 is operating (in the pH range studied, above pH 9):



(3)

The measured value K_s is related to the equilibrium constant of the addition of hydroxide ions (K) and to the dissociation constant of the hydrated form (K_1) by the expression $K_s = K_w K K_1(K + K_1)$ and to the dehydration constant K_{deh} = [ArCHO]/[ArCH(OH)$_2$] by relation $K_s = K_1/(1 + K_{deh})$. If, as indicated by the estimate of the hydration, $K_{deh} \ll 1$, then the measured value K_s is practically equal to K_1. The value of $pK_s \approx 11.2$ found for the two thiazole derivatives is of the same order of magnitude as values of dissociation constants of other compounds bearing the hydrated aldehydic group in the vicinity of an electronegative grouping (e.g., pK_1 about 10.0 for chloral[23] and trifluoroacetophenone[24] and 11.4 to 12.15 for the three pyridinecarboxaldehyde *N*-oxides[18]).

For 2-imidazolecarboxaldehyde dissociation of the NH group (Table II) and of the geminal diol (Table III) compete according to eq 4.

Formation of a new, more intense band at 310 nm in the pH range 9–11 indicates that paths 2a, 2b, and also 3a, 3b are not main contributors. The measured value of pK_N (Table II) is thus affected primarily by equilibria 1a and 4a. Consequently, the second acid–base process (pK_s in Table III) corresponds predominantly to equilibria 1b and 4b. For evaluation of relative contribution of path 1 and 4 information on position of hydration–dehydration equilibria both in neutral molecules and in imidazolate ions is essential.

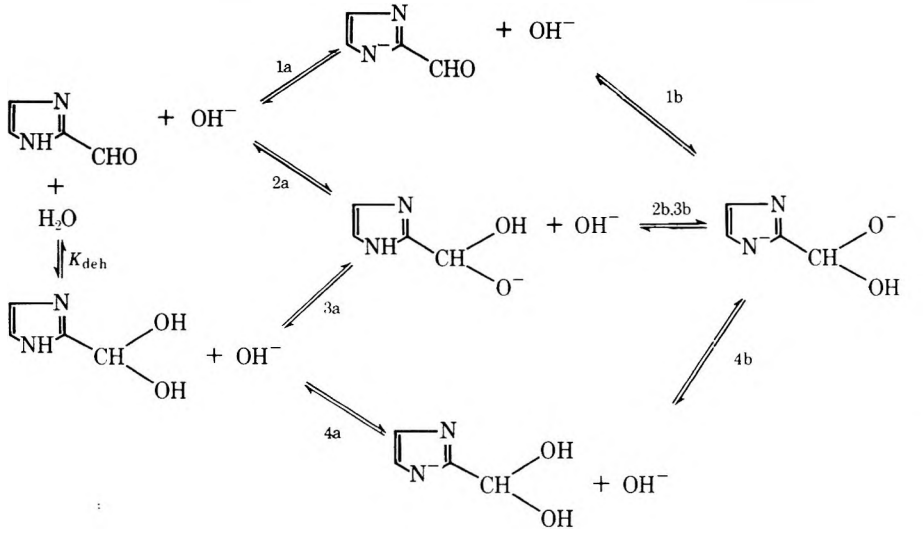
Anodic waves of the hydrated aldehydes (Table III) resembled those obsered for pyridinecarboxaldehydes[25] and correspond probably to the same process, i.e., oxidation of the geminal diol anion to carboxylic acid.

Structural Effects. Any comparison of structural effects on values of equilibrium constants and half-wave potentials (Tables I–III) must be carried out only inside of each of the specified groups, as only inside each of the groups the processes involved are analogous and hence the values measured comparable. This restricts the number of comparable compounds so that no attempt has been made to apply linear free energy or other theoretical treatment.

For addition of hydroxide ions to nonhydrated aldehydes (Table I) introduction of electropositive substituents into furan and thiophene rings results in an increase in pK' value, whereas electronegative substituents exert opposite effect. This is the same direction as observed for substituted benzaldehydes[13] and indicates a positive value of the reaction constant ρ. The difference in reactivity between fural and 2-thiophenecarboxaldehyde is relatively small, but both these aldehydes are considerably more reactive toward OH^- addition than N-substituted 2-pyrrolecarboxaldehydes. Extension of the condensed aromatic system in the carbazole derivative results in a marked shift in favor of the adduct.

Effect of substituents on the half-wave potentials of both furan and thiophene derivatives is small (Table I). Oxidation of 2-thiophenecarboxaldehydes occurs at somewhat more negative potentials (indicating easier oxidation) than that of fural and its derivatives. Half-wave potentials of 2-thiophenecarboxaldehyde are very close to those of benzaldehyde (Figure 1), indicating a similar level of interaction between the aromatic ring and the side chain.

Both N-substituted 2-pyrrolecarboxaldehydes and the carbazole derivative are oxidized at more positive potentials than furan and thiophene derivatives. The difference between N-substituted pyrrole and carbazole derivatives is relatively small, indicating that the conjugation extending effect of the



(4)

annelled rings is counterbalanced by another effect. The latter may be an effect of most suitable orientation at the electrode surface in the course of the electrode process, which the rigid carbazole derivative cannot achieve.

The value of pK_N for 3-indolecarboxaldehyde[14] has been shown to deviate from pK_N–σ plot, even when $\sigma^-_{p\text{-CHO}}$ was used. When the value of pK_N for 2-indolecarboxaldehyde (Table II) was correlated with $\sigma^-_{p\text{-CHO}}$, $\sigma_{m\text{-CHO}}$, or $(\sigma_p + \sigma_m)_{CHO}/2$, a small deviation in the same direction as for the 3-formyl derivative was observed. This clearly indicates a type of interaction between the formyl group and the indole ring, different from the interaction between the aniline ring and the aldehydic groups as expressed in the value of $\sigma^-_{p\text{-CHO}}$.

Specific interaction, not expressed by substituent constants, between the aldehydic group and the heterocycle is shown also by the comparison of the effect of an annelled benzene ring. Whereas pK_N value for the unsubstituted pyrrole is *0.54 units larger* than that for indole,[14] the effect of the annelled benzene ring on pK values of 2-carboxaldehydes is just opposite (Table II): the pK_N value for the pyrrole derivative is *0.35 units smaller* than that of the indole compound. In addition to the type of interaction observed for the 3-indolecarboxaldehyde[14] which would be in pyrrole even stronger than in indole (assuming comparable values of reaction constant ρ), it is impossible for the 2-carboxaldehydes to rule our direct interaction between the formyl group and the heterocyclic nitrogen.

The interaction between the formyl group and the indole ring, which increases the reactivity toward the OH^- attack on the NH group, seemingly decreases the reactivity of the formyl group to oxidation. This is shown by the absence of electroactivity of 3-indolecarboxaldehyde. Smaller interaction is shown by the 2-indolecarboxaldehyde, the electroactivity of which has not been impaired. Also the increase in the reactivity toward oxidation from pyrrole to indole derivative (Table II) is in the expected direction. Available data for these compounds do not allow us to distinguish if the changes in potentials are due to changes in formation of the electroactive geminal diol anion, in the electron transfer, or the hydrogen abstraction and more detailed analysis must be postponed.

All these results, nevertheless, indicate interaction between the formyl group and the indole ring, stronger for the 3 isomer than for the 2 isomer. Nevertheless, as such interaction operates not only in the 3 isomer, but also in the 2-carboxaldehyde it is indicated that the explanation by enol formation, offered for 3-carboxaldehyde,[14] might not be complete.

Presence of a unit negative charge on the heterocyclic ring decreases reactivity toward the hydroxide attack on the carbonyl group in a similar way as N-substitution. This follows from comparison of pK' values in Table II with values for N-substituted pyrrole derivatives (Table I).

For hydrated aldehydes the small effect of the annelled benzene ring in the thiazole derivatives as well as of *N*-methyl substitution in 2-imidazolecarboxaldehyde on values of pK_s (Table III) is probably due to the absence of conjugation in both the predominating geminal diol and its anion.

On the other hand, the ease of oxidation is increased by the added benzene ring in the 2-benzothiazolecarboxaldehyde and decreased by N-methylation in the imidazole derivative, as follows from comparison of polarographic half-wave potentials (Table III). As such change cannot reflect the position of the equilibrium yielding geminal diol anion, it must be caused by structural effects either on the electron transfer or hydrogen abstraction.

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Nucleophilic Additions to Aldehydes and Ketones. 3.[1] Reactions of Ortho-Substituted Benzaldehydes and Their Polarographic Oxidations

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Ortho-substituted benzaldehydes add in strongly alkaline media hydroxide ions in a reversible, rapidly established equilibrium reaction, in which an anion of the geminal diol [$ArCH(OH)O^-$] is formed. Extrapolation to zero ionic strength and use of acidity function J_- made it possible to determine thermodynamic equilibrium constants for benzaldehydes bearing both electropositive and electronegative substituents. Correlation of pK_a with $\sigma_{o\text{-}X}$ and dissociation constants of benzoic acids were explained by similarity in structures of the geminal diol anion and carboxylate ion or the transition state in ester hydrolysis. Structural effects on polarographic half-wave potentials of anodic waves indicated quantitative or qualitative changes in the heterogeneous portion of the electrode process, seemingly involving the hydrogen abstraction step [$ArCH(OH)O^- \rightleftharpoons ArCOOH + 2e + H^+$].

Previously[1,3] the acidity scale J_- for reactions involving addition of hydroxide ion in strongly alkaline media has been used for determination of thermodynamic values of equilibrium constants for additions to meta- and para-substituted benzaldehydes[3a] as well as to some heterocyclic aldehydes.[1] In this paper the study was extended to some ortho-substi-

Table I. Spectral Properties and Equilibrium Constants K for the Addition of Hydroxide Ions to Benzaldehydes Substituted in Ortho Position by X

No.	X	Registry no.	λ_{max}, nm	ϵ, l/mol cm	pK^a (overlap)	p$\bar{K}^d$	pK'^e (overlap)	pK'^f (J_- plots)	Δ^g	p$K_{COOH}{}^h$	$\sigma_{p\text{-}X}{}^i$	$\sigma_{o\text{-}X}{}^k$
1	OC_2H_5	613-69-4	257	9800	+1.18[b]		15.18[b]	15.30	0.12	4.21	−0.25	−0.35
2	COO^-	58502-59-3	255	7700	+1.14[b]		15.14[b]	15.31	0.17	5.51	+0.13	
3	$CH(CH_3)_2$	6502-22-3	262	14200	+0.99[b]		14.99[b]	15.21	0.22	3.64	−0.20	
4	OCH_3	135-02-4	257	10500	+0.96[b]		14.96[b]	15.15	0.19	4.09	−0.27	−0.39
5	H	100-52-7	250	12800	+0.90[b]		14.90[b]			4.19	0.00	0.00
6	CH_3	529-20-4	260	11700	+0.86[b]	+1.03	14.86[b]	15.10	0.24	3.92	−0.17	−0.17
7	I	26260-02-6	258	6700	−0.33[c]		13.67[c]	13.83	0.16	2.66	+0.27	+0.21
8	Cl	89-98-5	254	8800	−0.36[c]	−0.41	13.64[c]	13.81	0.17	2.92	+0.23	+0.20
9	Br	6630-33-7	256	8800	−0.41[c]		13.59[c]	13.80	0.21	2.85	+0.23	+0.21
10	F	446-52-6	246	12300	−0.44[c]		13.56[c]	13.78	0.22	3.27	+0.06	+0.24
11	CF_3	447-61-0	246	8800	−0.59[c]		13.41[c]	13.45	0.04		+0.55	
12	NO_2	552-89-6	260	12800	−1.11[c]	−1.03	12.89[c]	13.01	0.12	2.21	+0.78	+0.80

[a] $K = C_{ArCH(OH)O^-}/C_{ArCHO}C_{OH^-} \times y_{ArCH(OH)O^-}/y_{ArCHO}\, y_{OH^-}$. [b] Values obtained by overlap procedures using compounds 7–12 as reference. [c] Values obtained by extrapolation to zero ionic strength. [d] $\bar{K} = C_{ArCH(OH)O^-}/C_{ArCHO}C_{OH^-}$; nonthermodynamic values reported by Greenzaid.[4] [e] pK' = pK + pK_w. [f] Values of pK_a obtained by means of J_- acidity function. [g] Difference between values obtained by means of J_- and the overlap procedure. [h] Dissociation constants of corresponding benzoic acids in water at 25 °C. [i] Hammett substituent constants. [k] Taft substituent constants based on ester hydrolysis.

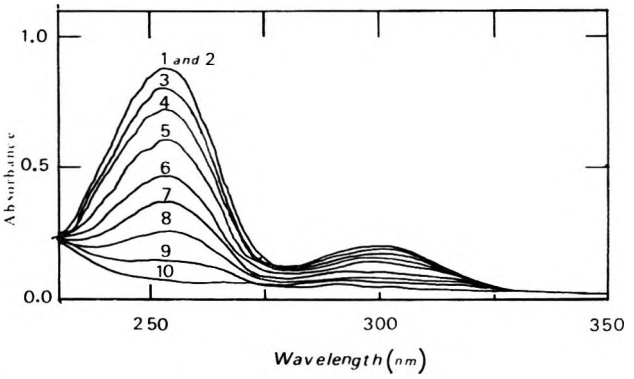

Figure 1. The uv spectra of 1×10^{-4} M o-chlorobenzaldehyde at 25 °C in aqueous (1% ethanol) sodium hydroxide solutions of the following molar concentrations: 2, 0.01; 3, 0.05; 4, 0.1; 5, 0.2; 6, 0.4; 7, 0.6; 8, 1.0; 9, 2.0; 10, 5.0. Curve 1 phosphate buffer, pH 10.

tuted benzaldehydes. Greenzaid[4] reported crude practical equilibrium constants for three monosubstituted ortho benzaldehydes. It was attempted to compare thermodynamic values of equilibrium constants with his data and to include a wider variety of both electropositive and electronegative substituents than could be studied by Greenzaid, whose treatment made it impossible to study solutions containing more than 1.5 M base.

As it has been proved[5] that the geminal diol anion is the reactive species in electrooxidation of benzaldehydes in alkaline media and a linear relationship between the polarographic half-wave potentials[6] and Hammett substituent constants σ has been confirmed for meta- and para-substituted benzaldehydes, the electrooxidation of ortho-substituted benzaldehydes and the effect of the nature of the substituent have been investigated as well.

Experimental Section

Chemicals. Benzaldehydes used were commercial products (Aldrich Chemical Co., Milwaukee, Wis.), freshly redistilled or recrystallized. Their purity was checked by gas–liquid chromatography. Stock solutions (0.01 M) of these aldehydes were prepared freshly each day in 96% ethanol. The origin of sodium hydroxide and preparation of solutions was the same as in part 2 of this series.[1]

Apparatus. Spectrophotometric and polarographic equipment used was the same as in part 2.[1] The capillary used had in 1 M potassium chloride at 0.0 V (vs. SCE), rate of flow $m = 2.2$ mg s^{-1} and drop time $t_1 = 3.1$ s at height of mercury column $h = 65$ cm.

Procedures. Recording of the uv spectra, polarographic curves, and measurement of half-wave potential was carried out as described in part 2.[1] The logarithmic analysis of polarographic curves was carried out by current measurement obtained with curves recorded at a slow rate of scanning (1 mV/s) to prevent hysteresis effects.

Evaluation of Equilibrium Constants. To determine the value of equilibrium constant K for reaction 1

$$ArCHO + OH^- \rightleftharpoons ArCH(OH)O^- \quad (1)$$

absorbance in the region between 250 and 280 mn was measured. The anions of the geminal diols formed in reaction 1 are for the majority of benzaldehydes studied practically transparent in this wavelength region (Figure 1), with the exception of o-nitrobenzaldehyde. Absorbance in this wavelength region is thus for most aldehydes a linear function of the concentration of the free aldehydic form. Molar absorptivity coefficients of these forms were obtained in buffers pH 10 where formation of the anion can be neglected (Figure 1). For o-nitrobenzaldehyde the decrease of the absorption band at 260 nm was accompanied by an increase of a band at 335 nm corresponding to the absorption of the nitrobenzene portion of the geminal diol anion with a resulting isosbestic point at 311 nm. As no change in the absorbance at 260 nm in 5 and 10 M sodium hydroxide was observed, this value was taken for the residual absorbance.

Values of the ratio $C_{ArCH(OH)O^-}/C_{ArCHO}$ were obtained by means of eq 2

$$C_{ArCH(OH)O^-}/C_{ArCHO} = (A_0 - A)/(A - A_r) \quad (2)$$

where A_0 is the absorbance of the aldehyde form ArCHO, A_r the residual absorbance of the anion $ArCH(OH)O^-$ (practically zero for all derivatives except o-nitro), and A the absorbance of the solution at any given sodium hydroxide concentration (all measured at a given wavelength).

Results

Thermodynamic values of equilibrium constants of reaction 1 were obtained in three different ways.

For compounds 7–12 (Table I) where the value of pK is less than zero, values of log $(C_{ArCH(OH)O^-}/C_{ArCHO}) - \log C_{OH^-}$ were plotted against C_{OH^-}. Extrapolation of such linear plots to zero ionic strength (i.e., to $C_{OH^-} = 0$) gave thermodynamic values of K (Table I).

For benzaldehydes 1–6 with pK values greater than zero the overlap procedure[8] was used. Because of the large gap between pK values of compounds 7–12 and 1–6, pK values for the latter were used successively as a reference value pK for each of the compounds 7–12. Averages of these values are reported in Table I.

To convert measured equilibrium constants (K) for hydroxide ion addition to a more conventional scale for hydrogen

Table II. Polarographic Half-Wave Potentials[a] (vs. SCE) of Benzaldehydes Substituted in Ortho Position by X in Sodium Hydroxide Solutions of Varying Molarity

X	0.01 M	0.03 M	0.1 M	0.3 M	1.0 M	3.0 M	5.0 M	7.0 M	pK'[b] (overlap)	$dE_{1/2}/dJ_-$[c]
F	−0.146	−0.156	−0.192	−0.251	−0.275	−0.327	−0.342		13.56	−0.068
Cl	−0.130	−0.162	−0.213	−0.251	−0.291	−0.339	−0.330		13.64	−0.077
Br	−0.154	−0.183	−0.221	−0.257	−0.305	−0.348	−0.346		13.59	−0.071
I	−0.140	−0.186	−0.208	−0.273	−0.273	−0.300	−0.327		13.67	−0.076
CF_3						−0.147	−0.227		13.41	
NO_2	−0.176	−0.191	−0.216	−0.243	−0.269	−0.271	−0.304	−0.298	12.89	−0.044
OCH_3		−0.129	−0.146	−0.166	−0.202	−0.219	−0.274	−0.286	14.96	−0.050
OC_2H_5			−0.125	−0.145	−0.178	−0.192	−0.257	−0.274	15.18	−0.054
CH_3			−0.134	−0.157	−0.214	−0.287	−0.343	−0.357	14.86	−0.096
$CH(CH_3)_2$			−0.150	−0.189	−0.253	−0.325	−0.432		14.99	−0.101
COO^-						−0.150	−0.180	−0.217	15.14	−0.103
H			−0.193	−0.230	−0.295	−0.393	−0.454	−0.450	14.90	−0.114

[a] Half-wave potentials measured against a carbon rod cathode, expressed relative to the half-wave potential of the unsubstituted benzaldehyde for which the values vs. SCE have been reported.[5] [b] pK' values determined by the overlap procedure (Table I). [c] Slope of the linear portion of the $E_{1/2}$–J_- plot in the J_- region where the half-wave potentials are shifted to more negative values with increasing J_- (Table III).

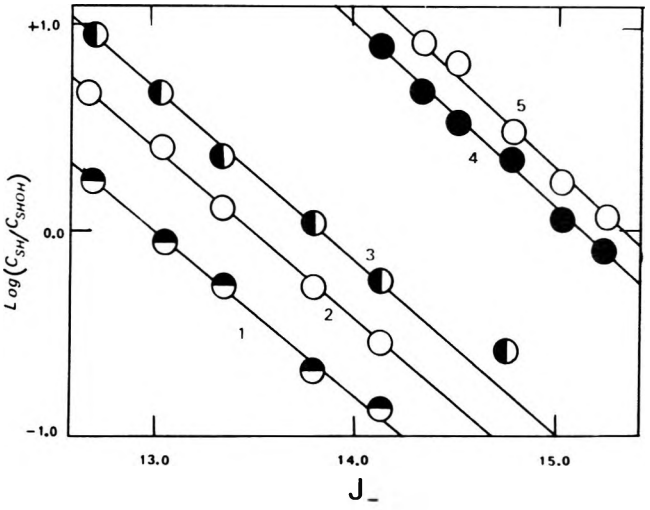

Figure 2. Values of log (C_{SH}/C_{SHOH^-}) determined from spectrophotometric results plotted against the J_- scale: 1, *o*-nitrobenzaldehyde; 2, *o*-trifluoromethylbenzaldehyde; 3, *o*-iodobenzaldehyde; 4, *o*-tolualdehyde; 5, *o*-ethoxybenzaldehyde.

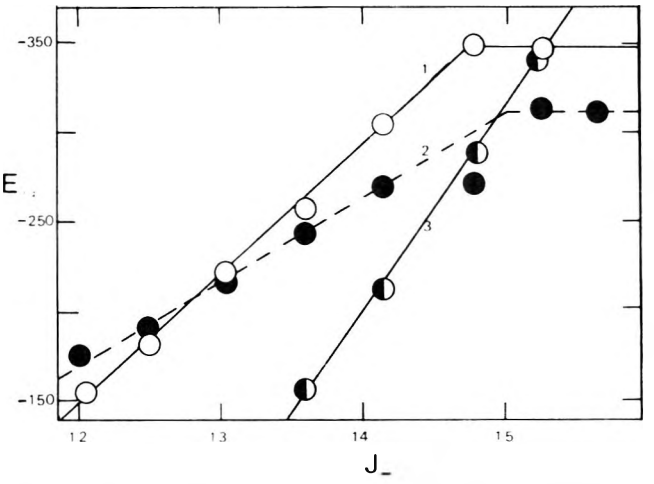

Figure 3. Dependence of half-wave potentials (mV vs. SCE) of substituted benzaldehydes on pH and acidity function J_-: 1, *o*-bromobenzaldehyde; 2, *o*-nitrobenzaldehyde; 3, *o*-tolualdehyde.

ion abstraction (pK'), the expression $pK' = pK + pK_w$ was used.

Alternatively, it was possible to use acidity function J_- established by means of meta- and para-substituted benzaldehydes[3b] using eq 3.

$$pK' = J_- - \log (C_{ArCH(OH)O^-}/C_{ArCHO}) \quad (3)$$

Systems which follow eq 3 must show a linear dependence of log ($C_{ArCH(OH)O^-}/C_{ArCHO}$) on J_- with a unit slope. Experimental values for ortho benzaldehydes gave linear plots (Figure 2) with slopes varying between 0.92 and 1.07. From the intercept of these linear plots at 50% conversion when $pK' = J_-$ values of pK' were obtained and are given in Table I.

The fulfillment of eq 3 indicates that all compared ortho-substituted benzaldehydes undergo the same type of nucleophilic addition (or acid/base) reaction as the meta- and para-substituted ones. No time change of spectra which would indicate a consecutive or side reaction was observed. The reversibility of the interaction with hydroxide ions was confirmed by partial acidification of the alkaline solution which produced the spectrum of the free aldehyde.

Polarographic anodic waves of the 12 ortho-substituted benzaldehydes studied corresponded to a two-electron oxidation process.[5,9] The limiting currents of these waves when corrected for the changes in viscosity ($i_{corr} = i_{meas} \times \eta^{1/2}$) were independent of sodium hydroxide concentration in the range 0.01 to 7 M. Half-wave potentials (Table II) were a function of pH and J_-. The $E_{1/2} - J_-$ (pH) plot shows two linear sections (Figure 3), shift at lower J_- and independence at higher J_- values. The intersection of the two linear parts was observed at J_- values somewhat larger than the pK' value. The slope $dE_{1/2}/dJ_-$ depends considerably on the nature of the substituent (Table II). Waves of *o*-carboxybenzaldehyde were measurable only at concentrations of sodium hydroxide higher than about 3 M; in the same region of strongly alkaline solutions the oxidation of *o*-trifluoromethyl derivative was also indicated, but the resulting wave was too indistinct for measurement.

Logarithmic analysis of the wave shape (Figure 4) gave linear plots of varying slope (Table III). No attempts have been made to study the anodic waves of ortho benzaldehydes at lower pH values by means of pulse polarography so that no information is available on shifts of half-wave potentials or the change in wave height in this pH region.

Discussion

Equilibria. Attempts to correlate quantitatively structural effects of ortho substituents on rates and equilibria can be

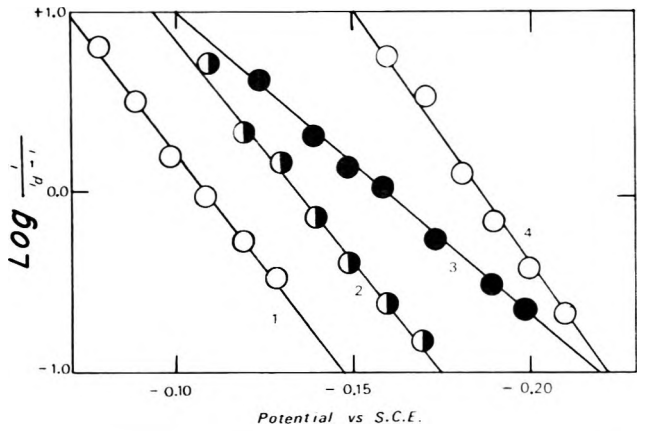

Figure 4. The logarithmic analysis of the rising portion of the anodic wave of ortho-substituted benzaldehydes. The value of log $(i/i_d - i)$ plotted against potential in volts: 1, *o*-tolualdehyde; 2, *o*-bromobenzaldehyde; 3, *o*-fluorobenzaldehyde; 4, *o*-iodobenzaldehyde.

Table III. Electrochemical Data for Oxidation of Benzaldehydes Substituted in Ortho Position by X Obtained in Alkaline Solutions

X	$dE_{1/2}/dJ_-$, V	$\beta n_a{}^a$ (0.058)/ $dE_{1/2}/dJ_-$	$dE/d \log (i/i_d - i)$, V	$\beta n_a{}^b$ (0.058)/ $dE/d \log (i/i_d - i)$
F	0.068	0.85	0.060	0.97
Cl	0.077	0.75	0.046	1.26
Br	0.071	0.82	0.039	1.49
I	0.076	0.76	0.036	1.61
NO_2	0.044	1.32	0.032	1.81
OCH_3	0.050	1.16	0.038	1.53
OC_2H_5	0.054	1.07	0.035	1.66
CH_3	0.096	0.60	0.041	1.41
$CH(CH_3)_2$	0.101	0.57	0.037	1.56
COO^-	0.103	0.56		
H	0.114	0.51	0.059	0.98

[a] Values obtained from shifts of half-wave potentials with sodium hydroxide concentration. [b] Values obtained from the slope of current-voltage curves.

classified into four categories: (a) attempts to correlate the rate or equilibrium constants of ortho-substituted compounds with Hammett substituent constants for corresponding para substituents ($\sigma_{p\text{-}X}$); (b) attempts to correlate such constants with a multiparameter equation, treating the ortho effects as additive to the polar effects; (c) attempts to correlate such constants with a special set of ortho-substituent constants ($\sigma_{o\text{-}X}$); (d) attempts to correlate them with equilibrium or rate constants for another reaction of ortho-substituted compounds.

The first approach is based on the qualitative assumption that electronic effects in para and ortho positions are not substantially different. The small difference between the role of the inductive effect in various positions on the benzene ring relative to the reactive center has been demonstrated,[10] so that the above assumption seems to equal the plausible conclusion that the resonance effect in para and ortho positions are not substantially different. Deviations from the log $K_{o\text{-}X}$–$\sigma_{p\text{-}X}$ plot can then be interpreted as one of the proximity effects due to steric hindrance of coplanarity, direct field effect, or effect of the large steric requirements of the ortho substituent.

The second approach assumes the additivity of steric effects and is thought to be confirmed by apparently improved correlation resulting from the introduction of a second term in a linear free energy relationship. It seems that even statisticians have problems with deciding what is a measure of better correlation when a further adjustable parameter is included, and hence, even when a statistical proof was offered,[11] it does not seem to be possible to decide with certainty whether the improvement of the correlation is apparent or real. Moreover, the assumption of general additivity of steric effects does not seem to be plausible, as direct interactions of adjacent groups will depend also on the size, steric requirements, polarizability, and charge of the reactive center—not only of the substituent.

The same type of arguments apply also to the introduction of a special set of ortho-substituent constants. This presumes that the inductive, resonance, and polar effects of the ortho group are additive and that the relative size of the steric group will be independent of the reaction series and analogous to the steric effect operating in the series chosen as reference.

The limitation of the fourth type of application is that correlation between equilibrium constants is restricted to reaction series where both the structures of the starting materials and of the products (and hence also of the transition states) were similar in both series compared. The similarity in structures in starting materials *and* products in both series is the key to the limits of such application. It seems that the differences in structures of the starting material and product may be relatively small for this application to be successful. It seems difficult to predict how small these differences can be, but even when such log $K^1{}_{o\text{-}X}$–log $K^2{}_{o\text{-}X}$ correlations are successful, their use will be restricted to a narrow range of reactions and universality—one of the main advantages of the linear free energy treatments—will be lost.

The values of pK' for reaction 1 (Table I) show acceptable correlation with $\sigma_{p\text{-}X}$ constants for $\rho = 3.50$ ($r = 0.92$ for 11 compounds). This indicates that steric effects in the addition of hydroxide ions to benzaldehydes are not predominant when compared with electronic effects. The only substantial deviation from the linear pK'–$\sigma_{p\text{-}X}$ plot was observed for the COO^- grouping, which shows a pK' value 1.5 larger than predicted by the pK'–$\sigma_{p\text{-}X}$ plot and similar to values obtained for branched o-alkyl or alkoxy derivatives. As even branched alkyl groups do not show any substantial steric effect on the pK' values, it can be concluded that the deviation results from the effect of aldehydic group on the carboxylate group rather than vice versa. Assumption of steric hindrance of coplanarity of the phenyl and carboxylate groups resulting in a loss of resonance interaction would explain why the change in pK' value due to an *o*-COO^- group is comparable to that caused by *o*-$CH(CH_3)_2$ or o-OR groups. Nevertheless, the competing effect of the negative unit charge cannot be excluded.

The correlation of pK' with $\sigma_{o\text{-}X}$ constants derived from the study of ester hydrolysis is comparable, with $\rho = 2.1$ and $r = 0.93$. This might indicate that the steric requirements in the transition state in ester hydrolysis [e.g., in $ArC(O^-)(OH)OR$] are comparable with those in the addition product [$ArC(O^-)(OH)H$].

Best correlation has been nevertheless obtained for comparison of pK' values of benzaldehydes with pK_{COOH} of ortho-substituted benzoic acids (Figure 5). Slope 1.25, $r = 0.96$, was obtained for ten compounds (for *o*-CF_3 no pK_{COOH} was found). The value for the ortho-carboxylate derivative was again observed to deviate. The pK' value was about one pK unit smaller than predicted by the pK'–pK_{COOH} plot. In this case it is nevertheless impossible to distinguish whether the deviation is caused predominantly by the steric hindrance in the benzaldehyde or by specific mutual interaction of the carboxylate groups in the second dissociation step of the o-phthalic acid. When the values for polysubstituted benzaldehydes reported by Greenzaid[4] (except for the 2,6-disubstituted ones) were included (Figure 5) the slope 1.34 and $r = 0.97$ were obtained. The effect of 2,6 disubstitution mentioned by Greenzaid[4] is probably due to a steric hindrance to coplanarity of the aldehydic group with the phenyl ring.

Greenzaid[4] first reported the linearity of the log K'–log

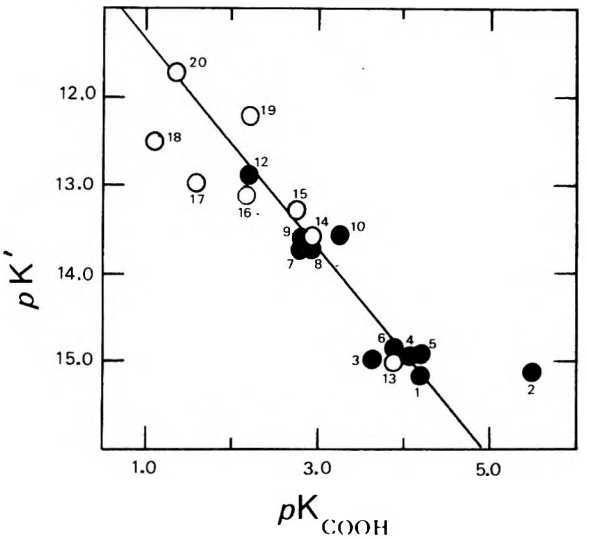

Figure 5. Dependence of pK' values for the addition of hydroxide ions to benzaldehydes on pK_{COOH} values for the corresponding benzoic acids. No. 1–12: our measurements, monosubstituted benzaldehydes, numbering see Table I; no. 13–20, values reported by Greenzaid[4] for 13, o-tolualdehyde; 14, o-chlorobenzaldehyde; 15, 2,4 dichlorobenzaldehyde; 16, o-nitrobenzaldehyde; 17, 2,6-dichlorobenzaldehyde; 18, 2-chloro-4-nitrobenzaldehyde; 19, 2-chloro-5-nitrobenzaldehyde; 20, 2,4 dinitrobenzaldehyde.

K_{COOH} plot for a limited range of substituents, but did not attempt to offer an explanation of the reasons for this correlation. We assume that the basis is the similarity in the steric requirements of the acid [ArC(=O)OH and ArC(=O)H] and the conjugate base [ArC(=O)O$^-$ and ArCH(O$^-$)OH] forms. Any future correlation can be expected only for structurally closely related series.

The differences between our values and the three values reported for monosubstituted ortho derivatives by Greenzaid (Table I) are small for the strongly electronegative, somewhat larger for the more electropositive substituents. This reflects the narrower range of hydroxide concentration over which Greenzaid[4] was able to carry out measurements.

Differences between our values obtained by the overlap procedure and based on J_- function reflect differences in the choice of "anchoring" compounds, which were compounds 7–12 in the overlap procedure, *m*- and *p*-nitro- and cyanobenzaldehydes in the definition of J_- acidity function. Even when the relative values are reliable to ±0.03 pK units, the absolute accuracy is not better than ±0.1 pK unit.

Electrooxidation. Based on a wide range of reaction series it was possible to prove repeatedly[6] that shifts of polarographic half-wave potentials with structure can be correlated with empirical substituent constants in a way analogous to treatments of rate or equilibrium constants. Conditions necessary for such treatment is that mechanism of all compared processes remains identical, that the transfer coefficient obtained from the shape of waves is either the same for all compounds compared or a linear function of the substituent constant involved. Furthermore, all the half-wave potentials compared must be either pH independent, the slope $dE_{1/2}$/dpH must be practically the same, or the slope must be a linear function of the particular substituent constant.

All these conditions are well fulfilled for half-wave potentials of meta- and para-substituted benzaldehydes. Consequently, a linear $E_{1/2}$–$\sigma_{m,p\text{-}X}$ plot was observed.[5] For ortho-substituted benzaldehydes the values of the transfer coefficient β obtained either from the wave shape or from the $E_{1/2}$–J_- plots varied widely for the substituents studied and were not a simple function of substituent constants $\sigma_{p\text{-}X}$ or $\sigma_{o\text{-}X}$. It is thus not surprising that no linear relationship has been found between the half-wave potentials and either $\sigma_{p\text{-}X}$, $\sigma_{o\text{-}X}$, or pK_{COOH} values.

The overall number of electrons transferred, the region of potentials in which the anodic waves were observed, and the shape of the $E_{1/2}$–pH(J_-) plots for ortho-substituted compounds were similar to those observed for meta- and para-substituted benzaldehydes. It is thus possible to conclude that the overall reaction scheme of the electrooxidation is in both cases similar and that the anion of the geminal diol [ArCH(OH)O$^-$] is the electroactive form.

Nevertheless, the considerable differences in the values of transfer coefficients indicate differences in the electrode process proper. The values of βn_a (Table III) not only vary according to the procedure used in obtaining them, but show variations even inside each group. These differences are smaller for values of βn_a obtained by logarithmic analysis of polarographic waves (Table III), where the majority of the compounds gives βn_a between 1.49 and 1.66, the exception being the unsubstituted compound (βn_a = 0.98), *o*-F (0.97), o-Cl (1.26), and *o*-NO_2 (1.81). Larger variability of the value of βn_a obtained from shifts of $E_{1/2}$ with J_- seems to indicate formation of three groups: ortho halogens (βn_a = 0.75–0.85), ortho-alkyl substituted compounds together with unsubstituted benzaldehyde (0.51–0.60), and *o*-COO$^-$ and the remaining *o*-OCH_3, *o*-OC_2H_5, and *o*-NO_2 (1.07–1.32). The greater sensitivity of the values obtained from $E_{1/2}$–J_- plots seems to indicate that the difference among the ortho derivatives and between the ortho and meta/para derivatives is probably in the hydrogen abstraction step[5] [ArCH(OH)O$^-$ ⇌ ArCOOH + 2e + H$^+$). Nevertheless, until it is better understood why for some electrode processes the values of βn_a (or αn_a) obtained from shape and half-wave potential shifts are identical whereas for others (like benzaldehyde oxidations) different,[12] such conclusions must remain tentative.

Conclusions

The good structural correlations found for pK_a values and the hydroxide addition reaction and the poor ones found for half-wave potentials of ortho-substituted benzaldehydes indicate that the complication is in the heterogeneous rather than homogeneous component of the electrode process. The indication that steric effects can affect a heterogeneous process at the electrode surface more deeply than a homogeneous process in the solution (even when in a layer adjacent to the electrode) can contribute to investigations of heterogeneous electrode processes.

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Reaction of *N,N*-Dimethyl-2-triorganosilylethylamines with Benzyne

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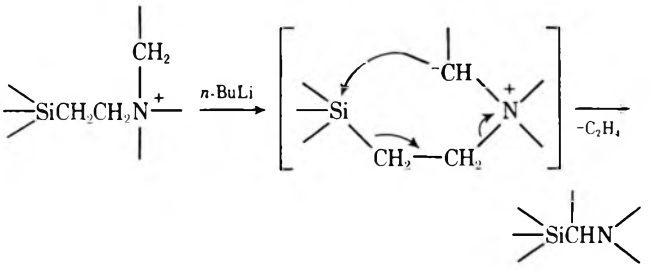
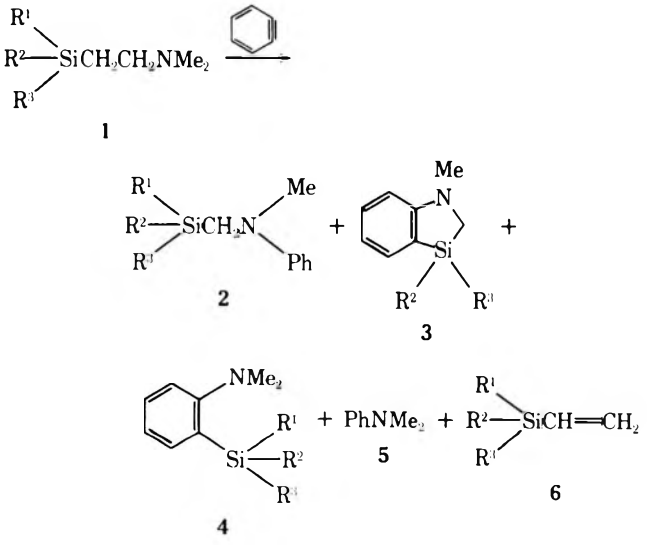
Reaction of *N,N*-dimethyl-2-triorganosilylethylamines (**1a–d**) with benzyne, produced from o-fluorobromobenzene and *n*-butyllithium, gave *N*-methyl-*N*-triorganosilylmethylanilines (**2a–d**), 1-methyl 3,3-disubstituted benzo[*d*]-1,3-azasilolines (**3b–d**), *N,N*-dimethylaniline (**5**), and triorganovinylsilanes (**6a–d**). It was revealed that the cyclization giving **3** was induced in the presence of excess *n*-butyllithium. The reaction mechanism also is discussed.

In our earlier paper[1] dealing with the reaction of β-triorganosilylethylammonium iodides with *n*-butyllithium, it was shown that 1,4-anionic rearrangement of the triorganosilyl groups from carbon to carbon occurred in the ylide intermediates to give *N*-triorganosilylmethylamines. Ammonium



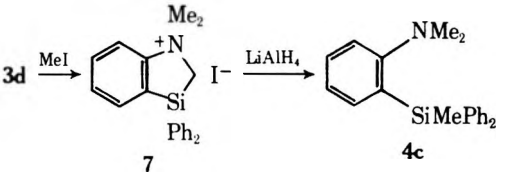
ylides can be formed by the reaction of tertiary amines with benzynes or carbenes, as well as by treatment of quaternary ammonium salts with strong bases.[2] The present paper describes the reaction of *N,N*-dimethyl-2-triorganosilylethylamines (**1**) with benzyne produced by the reaction of *o*-fluorobromobenzene with *n*-butyllithium.

Scheme I

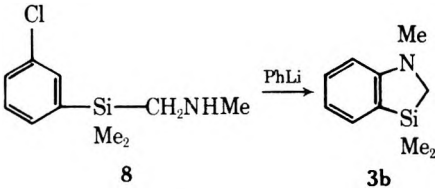


Addition of *o*-fluorobromobenzene to a mixture of *N,N*-dimethyl-2-trimethylsilylethylamine (**1a**) and 3 mol of *n*-butyllithium, upon workup, gave *N*-methyl-*N*-trimethylsilylmethylaniline (**2a**), *N,N*-dimethylaniline (**5**), and trimethylvinylsilane (**6a**). Their yields are shown in Table I. Formation of **2a** is regarded as a result of the 1,4-anionic rearrangement of the trimethylsilyl group in an ylide intermediate (**11**) produced by proton transfer from the first betaine intermediate (**9**) (path b in Scheme II), and **5** and **6** could be the Hofmann elimination products through another betaine intermediate (**10**) (path a).

However, a similar treatment of *N,N*-dimethyl-2-triphenylsilylethylamine (**1d**) with benzyne gave an unexpected amine (**3d**) with a small amount of the expected rearrangement product, *N*-methyl-*N*-triphenylsilylmethylaniline (**2d**). Elemental, NMR, and mass spectral analyses of **3d** suggested its structure as 1-methyl-3,3-diphenylbenzo[*d*]-1,3-azasiloline. Lithium aluminum hydride reduction of the methiodide (**7**) of **3d** gave a high yield of *o*-methyldiphenylsilyl-*N,N*-dimethylaniline (**4c**), which was identical with an authentic sample prepared by reaction of o-bromo-*N,N*-dimethylaniline with methyldiphenylchlorosilane in the presence of *n*-butyllithium. In a previous paper[3] we showed that $SiCH_2$–N^+ bonds were cleaved more readily by lithium aluminum hydride reduction than CH_3–N^+ bonds in 1,2,3,4-tetrahydrobenzo[*d*]-1,3-azasiline methiodides.



The reaction of *N,N*-dimethyl-2-dimethylphenylsilylethylamine (**1b**) or *N,N*-dimethyl-2-methyldiphenylsilylethylamine (**1c**) with benzyne also gave *N*-methyl-*N*-dimethylphenyl- (or methyldiphenyl-) silylmethylaniline (**2b** or **2c**) and 1,3,3-trimethyl- (or 1,3-dimethyl-3-phenyl-) benzo[*d*]-1,3-azasiloline (**3b** or **3c**), respectively. Compound **3b**



proved identical with one of the reaction products between (3-chlorophenyl)methylaminomethyldimethylsilane (**8**) and phenyllithium.

It is improbable that the cyclization product (**3**) is produced directly from the betaine (**9**) or ylide (**11**) intermediate. The presence of excess *n*-butyllithium used should cause the formation of **3**. In fact when the reaction was carried out using an equimolar amount of *n*-butyllithium, a small amount of **3d** was obtained instead of an increase in the yield of **2d**. Elevation of the reaction temperature from −50 to −10 °C induced again an increase in the yield of **3d** and a decrease in **2d**.

It is known that metalation of *N,N*-dimethylaniline by *n*-butyllithium takes place at the ortho position,[4] and that cyclization of 4-triphenylsilylbutyllithium to 1,1-diphenylsilolane occurs at −25 °C with elimination of phenyllithium.[5] On the basis of these experimental results, it seemed reasonable to assume that the cyclization reaction giving **3** proceeded via the rearrangement product (**2**). However, no reaction was observed between **2d** and *n*-butyllithium under the reaction condition.

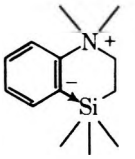
Table I. Reaction Products of *N,N*-Dimethyl-2-triorganosilylethylamines (1a–d) with Benzyne

				Reaction conditions			Yield,[a] %					
	R^1	R^2	R^3	*n*-BuLi, mol	Temp, °C	Time, h	2	3	4	5	6	1 (recovery)
a	Me	Me	Me	3	−50 to −55	6	33.6 (36.3)	0	0	15.1 (16.4)	9.1 (9.9)	7.5
b	Ph	Me	Me	3	−50 to −55	6	24.7 (34.1)	18.6 (25.8)	0	6.6 (9.1)	7.0 (9.7)	27.5
c	Ph	Ph	Me	3	−50 to −55	6	5.0 (6.6)	24.0 (31.8)	6.7 (8.8)	9.3 (12.2)	10.0 (13.1)	23.5
d	Ph	Ph	Ph	3	−50 to −55	6	5.1 (6.2)	24.6 (29.8)	0	20.0 (24.0)	25.9 (31.4)	17.8
				1	−50 to −55	6	29.7 (33.9)	Trace	0	37.5 (46.8)	49.6 (56.7)	12.7
				1	−10 to −15	3	Trace	21.2 (21.4)	0	40.9 (41.3)	55.5 (55.9)	9.1
				3[b]	−50 to −55	6	35.1 (45.3)	8.1 (10.5)	0	30.7 (39.6)	20.2 (26.0)	22.5

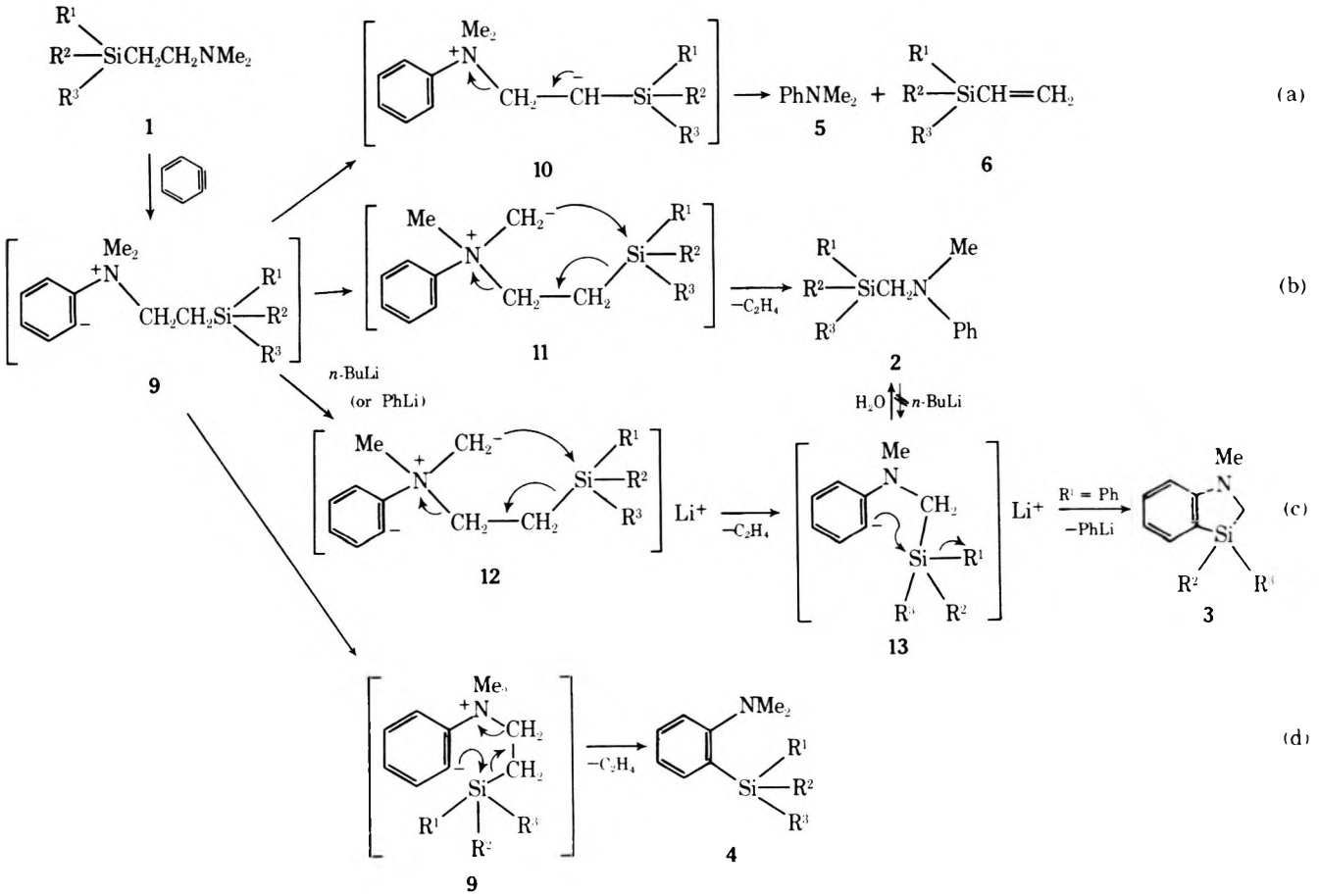
[a] Yields in parentheses are based on unrecovered **1**. [b] This reaction was carried out by addition of *n*-butyllithium, contrary to the other reactions, to a mixture of **1d** and *o*-fluorobromobenzene.

When 3 mol of *n*-butyllithium was added, contrary to the above-mentioned procedures, to a mixture of **1d** and *o*-fluorobromobenzene, the yield of **2d** was increased but **3d** was decreased (see Table I). This result suggests that the presence of excess *n*-butyllithium is required at the initial stage of the reaction but not the final stage for the formation of **3**.

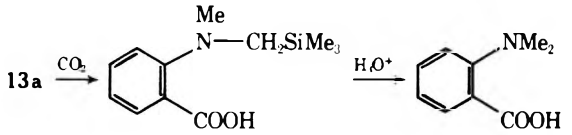
The formation of **3** may proceed by the following steps. Deprotonation by excess *n*-butyllithium takes place in part of the first intermediate (**9**), in which the betaine carbanion is presumably stabilized by coordination with the silicon atom, to give the second intermediate (**12**). Subsequently **12** is converted into the third intermediate (**13**) by silyl rearrangement with loss of ethylene. Then the cyclization reaction of **13** gives **3** with elimination of phenyllithium. When an equimolar amount of *n*-butyllithium was employed at −10 °C, this phenyllithium could be available as the deprotonating agent from **9** to **12**.



Scheme II

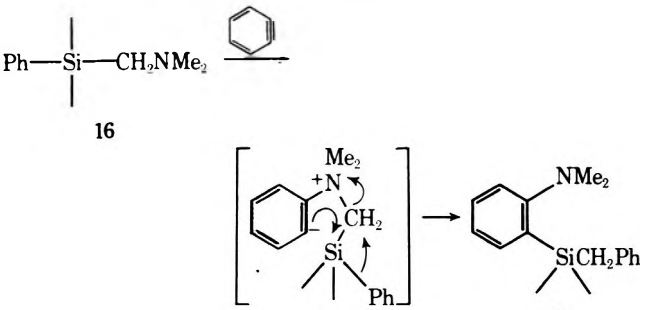


If the postulated reaction path is reasonable, the third intermediate (**13a**) having no phenyl substituent on the silicon atom, which is converted into **2a** by addition of water, should have remained in the reaction mixture, because an alkyl substituent is not easily cleaved from silicon by nucleophilic reagents.[6] Addition of carbon dioxide to the reaction mixture from **1a** with benzyne gave *o*-(*N*-methyl-*N*-trimethylsilylmethylamino)benzoic acid (**14**), which produced *o*-(dimethylamino)benzoic acid (**15**) upon acid hydrolysis.



14 **15**

In the reaction of dimethylaminomethylphenylsilanes (**16**) with benzyne, a new rearrangement of the silyl group toward the anion in betaine (**17**) was observed in our laboratory.[7] In spite of the fact that a similar rearrangement might be possible in the first intermediate (**9**), none or at best small amounts of the rearrangement products, *o*-triorganosilyl-*N*,*N*-dimethylanilines (**4**), were isolated. The low contribution of this reaction path (path d) could be explained by the rate of 1,5 rearrangement of the silyl group being slower than 1,4 rearrangement (path b and c), as suggested by West[8] on the basis of the studies of N,N'-anionic silyl rearrangement in N-silylated ethylenediamine and propylenediamine.



16 **17** **18**

Experimental Section

NMR spectra were recorded using a JNM-MH-100 (JEOL) spectrometer employing tetramethylsilane as internal standard. Ir spectra were taken on an IRA-2 (Jasco) spectrometer. Mass spectra were recorded using a M-52 (Hitachi) spectrometer. GLC analyses were performed on JGC-750FID and JGC-1100FID (JEOL) chromatographs using stainless steel columns with a nitrogen flow rate of 50 ml/min. Quantitative analysis of the reaction mixtures was carried out by the internal standard method. Fractional distillation was accomplished by a GKR-50 (Büchi) Kugelrohr distillation apparatus. All boiling points and melting points are uncorrected. *n*-Butyllithium, 15% in hexane, was obtained from Nakarai Chemicals Ltd., Kyoto. Ether and THF were dried by distillation from lithium aluminum hydride just prior to use.

***N*,*N*-Dimethyl-2-dimethylphenylsilylethylamine (1b).** A solution of dimethylphenylsilyllithium[9] prepared from dimethylphenylchlorosilane (25.6 g, 0.15 mol) and lithium clippings (3.1 g, 0.45 g-atom) in THF (150 ml) was added to an ice-cold solution of 2-dimethylaminoethyl chloride (6.46 g, 0.06 mol) in THF (50 ml). After 15 h of stirring at room temperature, the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl. The THF layer was separated and the aqueous layer was extracted with ether. The combined organic layer was concentrated, and the residue was extracted with 5% HCl. The acid extract was neutralized with potassium carbonate and extracted with ether. Distillation of the ethereal extract gave 5.30 g (42.6%) of **1b**: bp 129–131 °C (30 mm); NMR ($CDCl_3$) δ 0.28 (s, 6, $SiCH_3$), 0.90–1.12 (m, 2, $SiCH_2$), 2.20 (s, 6, NCH_3), 2.20–2.42 (m, 2, NCH_2), 7.18–7.60 (m, 5, aromatic H); picrate, mp 135–137 °C (recrystallized from ethanol).

Anal. Calcd for $C_{18}H_{24}N_4O_7Si$: C, 49.53; H, 5.54; N, 12.84. Found: C, 49.71; H, 5.58; N, 12.10.

***N*,*N*-Dimethyl-2-methyldiphenylsilylethylamine (1c).** In a manner similar to that described for **1b**, methyldiphenylsilyllithium [prepared from methyldiphenylchlorosilane (27.9 g, 0.12 mol) and lithium clippings (2.5 g, 0.36 g-atom)][10] and 2-dimethylaminoethyl chloride (7.44 g, 0.07 mol) were treated in THF (200 ml) giving 13.00 g (67.0%) of **1c**: bp 110–114 °C (0.06 mm); NMR ($CDCl_3$) δ 0.56 (s, 3, $SiCH_3$), 1.20–1.44 (m, 2, $SiCH_2$), 2.16 (s, 6, NCH_3), 2.24–2.50 (m, 2, NCH_2), 7.24–7.66 (m, 10, aromatic H); oxalate, mp 164–166 °C (recrystallized from ethanol).

Anal. Calcd for $C_{19}H_{25}NO_4Si$: C, 63.48; H, 7.01; N, 3.90. Found: C, 63.42; H, 6.93; N, 3.93.

Reaction of *N*,*N*-Dimethyl-2-trimethylsilylethylamine[1] (1a) with Benzyne. A. A solution of *o*-fluorobromobenzene (2.31 g, 13 mmol) in ether (10 ml) was added within 5 min to a mixture of **1a** (1.74 g, 12 mmol) and *n*-butyllithium (25 ml, 39 mmol) in ether (60 ml) at −50 to −55 °C. After 6 h of stirring at the same temperature, the mixture was hydrolyzed with saturated aqueous NH_4Cl below −40 °C and extracted with ether. The ether layer was extracted with 5% HCl.

The HCl extract was neutralized with potassium carbonate and extracted with ether. The ethereal extract (basic part) was analyzed by GLC using a 3 mm × 1 m column filled with 30% Tergitol NP-35, programed from 60 to 200 °C at 6 °C/min. The chromatogram showed the presence of *N*-methyl-*N*-trimethylsilylmethylaniline (**2a**, 33.6%), *N*,*N*-dimethylaniline (**5**, 15.1%), and unchanged **1a** (7.5%). Samples of the products were isolated by fractional distillation and identified with authentic samples, respectively. Compound **2a**, bp 115–118 °C (15 mm) [lit.[1] bp 112–118 °C (13 mm)].

From the ether layer (neutral part), trimethylvinylsilane (**6a**, 9.1%) was detected and determined by GLC analysis (30% dioctyl sebacate, 3 mm × 3 m).

B. The above benzyne reaction was repeated. After 6 h of stirring, carbon dioxide was bubbled into the reaction mixture at −60 to −70 °C for 1 h, and then it was extracted with 5% NaOH. Dimethyl sulfate (3.8 g, 30 mmol) was added to the NaOH extract at room temperature. After 3 h of stirring, the mixture was extracted with ether. The ethereal extract was dried, concentrated, and distilled to give 90 mg (3.0%) of methyl *o*-(*N*-methyl-*N*-trimethylsilylmethylamino)benzoate: bp 150–155 °C (12 mm); NMR ($CDCl_3$) δ 0.10 (s, 9, $SiCH_3$), 2.80 (s, 2, NCH_2), 2.92 (s, 3, NCH_3), 3.96 (s, 3, OCH_3), 6.68–7.80 (m, 4, aromatic H); ir (neat) 1720 cm^{-1}.

Anal. Calcd for $C_{13}H_{21}NO_2Si$: C, 62.11; H, 8.42; N, 5.57. Found: C, 61.89; H, 8.20; N, 5.31.

Methyl *o*-(*N*-methyl-*N*-trimethylsilylmethylamino)benzoate (50 mg, 0.2 mmol) was dissolved in 30% HCl–EtOH (20 ml), and the mixture was heated under reflux for 12 h. After the addition of water (70 ml), the reaction mixture was made alkaline with 20% NaOH and washed with ether. The aqueous solution was neutralized with 10% HCl and extracted with chloroform to give 10 mg (30%) of *o*-(dimethylamino)benzoic acid (**15**).

Reaction of 1b with Benzyne. In a similar manner as described for **1a**, *o*-fluorobromobenzene (1.93 g, 11 mmol), **1b** (2.07 g, 10 mmol), and *n*-butyllithium (21 ml, 33 mmol) were allowed to react in ether (60 ml), and the reaction mixture was treated. GLC analysis (10% PEG-20M, 3 mm × 1 m, programmed from 80 to 250 °C at 6 °C/min) of the basic part showed the presence of **2b** (24.7%), **3b** (18.6%), **5** (6.6%), and unchanged **1b** (27.5%). Samples of the products were isolated by fractional distillation and characterized as follows.

1,3,3-Trimethylbenzo[*d*]-1,3-azasiloline (**3b**): bp 120–125 °C (28 mm); NMR ($CDCl_3$) δ 0.32 (s, 6, $SiCH_3$), 2.64 (s, 2, NCH_2), 2.88 (s, 3, NCH_3), 6.44–6.88 and 7.12–7.48 (m, 4, aromatic H).

Anal. Calcd for $C_{10}H_{15}NSi$: C, 67.73; H, 8.53; N, 7.90. Found: C, 67.45; H, 8.40; N, 7.85.

N-Methyl-*N*-dimethylphenylsilylmethylaniline (**2b**): bp 151–153 °C (6 mm); NMR ($CDCl_3$) δ 0.34 (s, 6, $SiCH_3$), 2.82 (s, 3, NCH_3), 3.06 (s, 2, NCH_2), 6.50–6.76 and 7.04–7.64 (m, 10, aromatic H).

Anal. Calcd for $C_{16}H_{21}NSi$: C, 75.23; H, 8.29; N, 5.48. Found: C, 75.10; H, 8.11; N, 5.30.

From the neutral part, dimethylphenylvinylsilane (**6b**, 7.0%) was detected and determined by GLC analysis (10% PEG-20M, 3 mm × 1 m).

Reaction of 1c with Benzyne. In a similar manner as described for **1a**, *o*-fluorobromobenzene (1.93 g, 11 mmol), **1c** (2.69 g, 10 mmol), and *n*-butyllithium (21 ml, 33 mmol) were allowed to react in ether (60 ml), and the reaction mixture was treated. Distillation of the basic part gave **5** (9.3%) and unchanged **1c** (23.5%). GLC analysis (10% Silicone AN-600, 3 mm × 1 m, programed from 110 to 250 °C at 6 °/min) of the neutral part showed the presence of **2c** (5.0%), **3c** (24.0%), **4c** (6.7%), and methyldiphenylvinylsilane (**6c**, 10.0%) (Compounds **2c**, **3c**, and **4c** were not extracted with 5% HCl.) Samples

of the products were isolated by fractional distillation and characterized as follows.

1,3-Dimethyl-3-phenylbenzo[*d*]-1,3-azasiloline (**3c**): bp 80–82 °C (0.03 mm); NMR ($CDCl_3$) δ 0.64 (s, 3, $SiCH_3$), 2.80 (s, 2, NCH_2), 2.90 (s, 3, NCH_3), 6.44–6.80 and 7.12–7.68 (m, 9, aromatic H).

Anal. Calcd for $C_{15}H_{17}NSi$: C, 75.26; H, 7.16; N, 5.85. Found: C, 75.11; H, 6.89; N, 5.79.

o-Methyldiphenylsilyl-*N,N*-dimethylaniline (**4c**): bp 140–145 °C (0.07 mm); mp 67–70 °C (recrystallized from hexane); NMR ($CDCl_3$) δ 0.84 (s, 3, $SiCH_3$), 2.28 (s, 6, NCH_3), 6.96–7.72 (m, 14, aromatic H)

Anal. Calcd for $C_{21}H_{23}NSi$: C, 79.44; H, 7.30; N, 4.41. Found: C, 79.30; H, 6.99; N, 4.16.

N-Methyl-*N*-methyldiphenylsilylmethylaniline (**2c**): bp 147–149 °C (0.07 mm); NMR ($CDCl_3$) δ 0.60 (s, 3, $SiCH_3$), 2.72 (s, 3, NCH_3), 3.38 (s, 2, NCH_2), 6.52–6.80 and 7.04–7.72 (m, 15, aromatic H).

Anal. Calcd for $C_{21}H_{23}NSi$: C, 79.44; H, 7.30; N, 4.41. Found: C, 79.26; H, 7.58; N, 4.43.

Reaction of *N,N*-Dimethyl-2-triphenylsilylethylamine[1] (1d) with Benzyne. A. In a similar manner as described for **1a**, *o*-fluorobromobenzene (1.93 g, 11 mmol), **1d** (3.32 g, 10 mmol), and *n*-butyllithium (21 ml, 33 mmol) were allowed to react in ether (60 ml), and the reaction mixture was treated. Distillation of the basic part gave **5** (20.0%) and unchanged **1d** (17.8%). GLC analysis (10% Silicone AN-600, 3 mm × 1 m, programmed from 150 to 300 °C at 6 °C/min) of the neutral part showed the presence of **2d** (5.1%), **3d** (24.6%), and triphenylvinylsilane (**6d**, 25.9%) (compounds **2d** and **3d** were not extracted with 5% HCl). Samples of the products were isolated by fractional distillation and characterized as follows.

1-Methyl-3,3-diphenylbenzo[*d*]-1,3-azasiloline (**3d**): bp 120–125 °C (0.01 mm); mp 92–93 °C (recrystallized from hexane); NMR ($CDCl_3$) δ 2.96 (s, 3, NCH_3), 3.10 (s, 2, NCH_2), 6.50–6.76 and 7.12–7.80 (m, 14, aromatic H); mass spectrum *m/e* 301 (M^+).

Anal. Calcd for $C_{20}H_{19}NSi$: C, 79.68; H, 6.35; N, 4.65. Found: C, 79.10; H, 6.13; N, 4.53.

N-Methyl-*N*-triphenylsilylmethylaniline (**2d**): bp 150–165 °C (0.01 mm); mp 73–74 °C (lit.[1] mp 73–74 °C).

B. The above reaction was repeated using an equimolar amount of *n*-butyllithium to give **2d** (29.7%), **3d** (trace), **5** (37.5%), **6d** (49.6%), and unchanged **1d** (12.7%).

C. The benzyne reaction described above for **B** was repeated at −10 to −15 °C. After 3 h of stirring, the reaction mixture was treated giving **2d** (trace), **3d** (21.2%), **5** (40.9%), **6d** (55.5%), and unchanged **1d** (9.1%).

D. *n*-Butyllithium (18 ml, 28 mmol) was added slowly over a 3-h period to a mixture of **1d** (2.98 g, 9 mmol) and *o*-fluorobromobenzene (1.75 g, 10 mmol) in ether (45 ml) at −50 to 55 °C, and stirring was continued for 3 h. The reaction mixture was treated giving **2d** (35.1%), **3d** (8.1%), **5** (30.7%), **6d** (20.2%), and unchanged **1d** (22.5%).

1,1-Dimethyl-3,3-diphenylbenzo[*d*]-1,3-azoniasiloline Iodide (7). A mixture of **3d** (0.13 g, 0.44 mmol) and methyl iodide (3 ml) in acetone (20 ml) was heated at 40–50 °C for 15 h. After removal of the acetone, the residue was recrystallized from ethanol to give 0.18 g (90.9%) of **7**, mp 187–188 °C.

Anal. Calcd for $C_{21}H_{22}INSi$: C, 56.89; H, 5.00; N, 3.16. Found: C, 56.78; H, 5.03; N, 3.06.

Lithium Aluminum Hydride Reduction of 7. A mixture of **7** (0.18 g, 0.4 mmol) and lithium aluminum hydride (0.1 g, 2.6 mmol) in THF (20 ml) was heated under reflux for 2 h. After the addition of saturated aqueous NH_4Cl, the THF layer was separated and the aqueous layer was extracted with ether. The combined organic layer was dried and concentrated. Recrystallization of the residue from hexane gave 0.12 g (94.5%) of **4c**, mp 68–70 °C.

***o*-Methyldiphenylsilyl-*N,N*-dimethylaniline (4c).** *n*-Butyllithium (5 ml, 7.8 mmol) was added to a solution of *o*-bromo-*N,N*-dimethylaniline (1.56 g, 7.8 mmol) in ether (40 ml) at 0–10 °C, and stirring was continued for 2.5 h at the same temperature. Then to the mixture was added a solution of methyldiphenylchlorosilane (1.63 g, 7 mmol) in ether (10 ml) at room temperature. After 3 h of heating under reflux, the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl and extracted with ether. The ethereal extract was dried and concentrated. Recrystallization of the residue from hexane gave 1.03 g (41.5%) of **4c**, mp 68–70 °C.

1,3,3-Trimethylbenzo[*d*]-1,3-azasiloline (3b). A solution of phenyllithium (33 mmol) in ether (20 ml) was added to a boiling solution of (3-chlorophenyl)methylaminomethyldimethylsilane (**8**, 6.40 g, 30 mmol) in ether (130 ml). After 2 h of heating, the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl and extracted with ether. Distillation of the extract gave 2.10 g (40%) of **3b**, which was identified by spectroscopic comparison with the sample obtained by the reaction of **1b** with benzyne.

Acknowledgment. The authors are grateful to the Shin-Etu Chemical Industry Co., Ltd., for a generous gift of chlorosilanes.

Registry No.—**1a**, 23138-94-5; **1b**, 58617-49-5; **1b** picrate, 58617-61-1; **1c**, 58617-50-8; **1c** oxalate, 58617-62-2; **1d**, 58617-51-9; **2b**, 58617-52-0; **2c**, 58617-53-1; **3b**, 58617-54-2; **3c**, 58617-55-3; **3d**, 58617-56-4; **4c**, 58617-57-5; **7**, 58617-58-6; **8**, 58617-59-7; 14 methyl ester, 58617-60-0; dimethylphenylsilyllithium, 3839-31-4; methyldiphenylsilyllithium, 3839-30-3; benzyne, 462-80-6; *o*-bromo-*N,N*-dimethylaniline, 698-00-0; methyldiphenylchlorosilane, 144-79-6.

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Formation of Vinylsilanes and Allylsilanes in Thermal Elimination Reactions of Esters of β-Hydroxyalkyltrimethylsilanes

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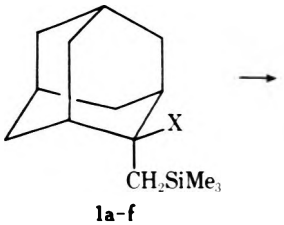
Thermolysis of esters of β-hydroxyalkyltrimethylsilanes $R_1R_2C(OH)CH_2SiMe_3$ was investigated as a route to the synthetically useful vinylsilanes $R_1R_2C{=}CHSiMe_3$. A survey of product composition vs. leaving group for esters of 2-trimethylsilylmethyl-2-adamantanol (**1a**) revealed exclusive alkene formation with a good leaving group and exclusive vinylsilane formation with a poor leaving group. Methanesulfonate ester **1f** decomposed under the conditions of its formation to give a 91% yield of methyleneadamantane (**2**). Thermolysis of 2-trimethylsilylmethyl-2-adamantyl *N*-phenylcarbamate (**1b**) at 160 °C produced 2-(trimethylsilylmethylene)adamantane (**3**) in 94% yield. Mixtures of **2** and **3** were obtained with other leaving groups. The vinylsilane 1-trimethylsilyl-3,3-dimethyl-1-butene (**9**) was obtained in 72% yield on thermolysis of 1-trimethylsilyl-3,3-dimethyl-2-butyl *N*-phenylthiocarbamate (**4c**). Mixtures of vinylsilanes and allylsilanes were obtained from esters which could eliminate in two directions. Thermolysis of 1-trimethylsilylmethyl-1-cyclohexyl *N*-phenylcarbamate (**5b**) or *S*-methyl xanthate (**5d**) gave the allylic silane 1-(trimethylsilylmethyl)cyclohexene (**12**) as the major product. Thermolysis of 1-trimethylsilyl-3-phenyl-2-propyl *N*-phenylthiocarbamate (**6c**) at 125 °C produced *trans*-1-trimethylsilyl-3-phenyl-1-propene (**13**) and *trans*-1-phenyl-3-trimethylsilyl-1-propene (**14**) in comparable amounts. Mixtures of the vinylsilane **15** and the allylsilane **16** were produced when 1-trimethysilyl-2-octanol (**7a**) was subjected to the Chugaev elimination sequence. *trans*-β-Styryltrimethylsilane was obtained in 43% yield on thermolysis of 1-phenyl-2-trimethylsilylethyl *N*-phenylcarbamate (**8b**), along with the product of ion-pair return, *N*-(1-phenyl-2-trimethylsilylethyl)aniline (**18**, 33%). The results are discussed in terms of ion-pair intermediates. Stabilization of the developing carbonium ion by carbon–silicon hyperconjugation requires the trimethylsilyl substituent to be anti to the leaving group. Retention of trimethylsilyl in the product is believed to occur because deprotonation of the carbonium ion by the anion of the leaving group is faster than rotation around the C(α)–C(β) bond with poorer (more basic) leaving groups. The ease of decomposition as a function of substrate structure (tertiary > secondary) and formation of ion-pair return products from **8b** and **8c** are consistent with this interpretation.

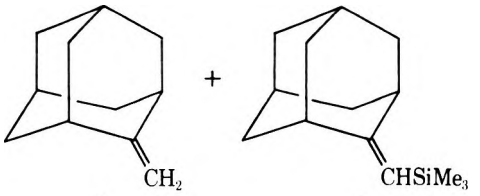
The readily available β-hydroxyalkyltrimethylsilanes, formed by addition of trimethylsilylmethylmagnesium chloride to aldehydes and ketones,[1] would appear to be useful substrates for the synthesis of vinylsilanes if methods could be developed to control the mode of their decomposition. Elimination reactions of β-functional organosilanes usually proceed with cleavage of the silicon–carbon bond to afford alkenes.[2] The few cases where vinylsilanes are produced are either heterogeneous reactions or are limited in terms of general applicability.[3]

Considerable recent interest has been shown in reactions of vinylsilanes directed toward synthetic applications. Potential utility in the synthesis of alkenes,[4] aldehydes,[5] ketones,[6] vinyl halides,[7] and in the annelation of ketones[8] has been demonstrated. Most of these efforts, as well as many mechanistic studies,[9] have focused on lightly substituted vinylsilanes.

The work reported here describes a study of the thermal decomposition of various esters of some β-hydroxyalkyltrimethylsilanes, performed with a view toward determining the factors which influence the relative proportions of vinylsilane and alkene formed. It was also hoped that such a study would provide a basis for developing a general method for converting β-hydroxyalkyltrimethylsilanes to vinylsilanes.[10]



1a-f



2 **3**

1a, X = OH
b, X = OC(O)NHPh
c, X = OC(S)NHPh
d, X = OC(S)SCH3
e, X = OSO2NHCO2CH3
f, X = OSO2CH3

Results

The β-hydroxyalkylsilanes utilized in this study were all prepared by addition of trimethylsilylmethylmagnesium chloride to the appropriate aldehyde or ketone and are listed in Table I.

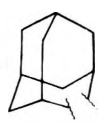
The system chosen for most detailed study was 2-trimethylsilylmethyl-2-adamantanol (**1a**). Elimination reactions in this system can lead only to methyleneadamantane (**2**) and 2-(trimethylsilylmethylene)adamantane (**3**), thereby simplifying analysis of the product mixtures and interpretation of the results.

The elimination reactions of the esters **1b–f** derived from **1a** were strikingly dependent on the nature of the leaving group.

Treatment of the anion of **1a** (generated with *n*-butyllithium) with methanesulfonyl chloride afforded directly on workup a 91% yield of methyleneadamantane (**2**) as the exclusive product.

Conversion of **1a** to its crystalline *N*-phenylcarbamate **1b** was effected by treatment of its alkoxide ion with phenyl isocyanate. Pyrolysis of the *N*-phenylcarbamate at 160 °C and distillation of the resulting liquid, followed by dilute acid extraction of aniline from the distillate, gave a 94% yield of the pure vinylsilane **3**. The vinylsilane was characterized by its NMR, ir, and mass spectra and elemental analysis (see Experimental Section for details).

Table I. β-Hydroxyalkyltrimethylsilanes Obtained by Addition of Trimethylsilylmethylmagnesium Chloride to Aldehydes and Ketones

Carbonyl compd	β-Hydroxyalkyl-trimethylsilane, $R_1R_2C(OH)CH_2SiMe_3$	Purified yield, %
2-Adamantanone	**1a**, $R_1 + R_2 =$ 	89
Pivaldehyde	**4a**, $R_1 = (CH_3)_3C$; $R_2 = H$	73
Cyclohexanone	**5a**, $R_1 + R_2 = -(CH_2)_5-$	86
Phenylacetaldehyde	**6a**, $R_1 = PhCH_2$; $R_2 = H$	35
1-Heptanal	**7a**, $R_1 = CH_3(CH_2)_5$; $R_2 = H$	84
Benzaldehyde	**8a**, $R_1 = Ph$; $R_2 = H$	83

Other thermal elimination sequences, Chugaev (xanthate ester),[11] Burgess (*N*-carbomethoxysulfamate ester),[12] and *N*-phenylthiocarbamate ester pyrolysis, were also examined and gave results intermediate between the two extremes with mixtures of **2** and **3** being produced. These results are summarized in Table II. Except in the case of the *N*-phenylcarbamate ester, the esters derived from **1a** could not be isolated but underwent decomposition to **2** and **3** under the conditions of their formation. The ratio **2**:**3** appears to parallel leaving group abilities, with greater proportions of the vinylsilane **3** being produced as the leaving group becomes poorer.

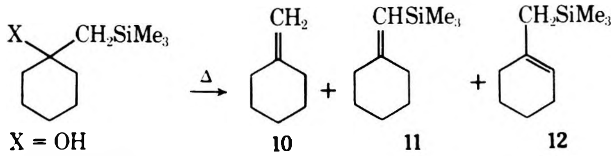
Encouraged by the efficient synthesis of **3** from **1b**, the thermolyses of esters of other β-hydroxyalkyltrimethylsilanes (**4a**–**8a**) were investigated. With the relationship between vinylsilane and alkene formation established by the study of esters of **1a**, extending the investigation to other systems was done with the objective of broadening the scope of vinylsilane synthesis. The reaction conditions used were those judged to have the best chance of success and no attempt was made to isolate the alkenes formed in competition with the vinylsilanes. Indeed, most of the alkenes are sufficiently volatile to present problems in isolation under the reaction and workup conditions employed.

The *N*-phenylcarbamate (**4b**) of 1-trimethylsilyl-3,3-dimethyl-2-butanol was more stable to thermolysis than **1b** and significant quantities of diphenylurea were produced along with a 28% yield of *trans*-1-trimethylsilyl-3,3-dimethyl-1-butene (**9**) after 30 h at 200 °C. Thermolysis of the more labile *N*-phenylthiocarbamate **4c** proved more satisfactory. The crystalline *N*-phenylthiocarbamate was sufficiently stable to be isolated, but underwent smooth decomposition at 140 °C to give the vinylsilane **9** in 72% yield. None of the cis vinylsilane could be detected by NMR analysis.

$(CH_3)_3CCH(X)CH_2SiMe_3 \xrightarrow{\Delta}$ *trans*-$(CH_3)_3CCH{=}CHSiMe_3$ (**9**)

4a, X = OH
b, X = OC(O)NHPh — 28%
c, X = OC(S)NHPh — 72%

The reactions of the corresponding esters of 1-trimethylsilylmethyl-1-cyclohexanol (**5a**) are more complicated in that an allylic silane (1-trimethylsilylmethylcyclohexene, **12**) can be formed as well as the vinylsilane (1-trimethylsilylmethylenecyclohexane, **11**) and the alkene (methylenecyclohexane, **10**).



	10	11	12
5a, X = OH			
b, X = CO(O)NHPh		12%	81%
d, X = OC(S)SCH$_3$		8%	55%
e, X = OSO$_2$NHCO$_2$CH$_3$			48%

Table II. Product Composition from Elimination Reactions of 2-Trimethylsilylmethyl-2-adamantyl Esters

Compd	X	Conditions	Yield of product, %[a] 2	3
1b	OC(O)NHPh	No solvent, 160 °C		94
1c	OC(S)NHPh	THF, 25 °C		73[b]
1d	OC(S)SCH$_3$	THF, 25 °C		44
			(28)[c]	(70)[c]
1e	OSO$_2$NHCO$_2$CH$_3$	Toluene, 110 °C	(51)[c]	(39)[c]
1f	OSO$_2$CH$_3$	THF, 25 °C	91	

[a] Isolated yields of purified product. [b] Determined by GLC to contain 3% of **2**. [c] Analytical yield determined by GLC vs. an internal standard.

As was the case with **1b** and **4c**, high conversion to silicon-containing products was observed in the thermolysis of the *N*-phenylcarbamate **5b**. The combined yield of the vinylsilane **11** and the allylic silane **12** was 93%. The allylic silane predominated over the vinylsilane by a ratio of 87:13. An identical ratio of **12** to **11** was obtained by the Chugaev route via **5d**, but the isolated yield was reduced to 63%. The two isomeric products **11** and **12** could not be separated by GLC and their ratio was determined by NMR analysis of the areas of the two trimethylsilyl resonances.

The yield of silicon-containing products decreased to 48% (quantitative GLC analysis vs. an internal standard) when the Burgess reagent was used with **5a**. Isolation of this product revealed it to be exclusively the allylic silane **12**, which was characterized by satisfactory analyses for C, H, and Si, and NMR and mass spectra consistent with the proposed structure (see Experimental Section).

The thermal elimination reactions of esters of 1-trimethylsilyl-3-phenyl-2-propanol (**6a**) and 1-trimethylsilyl-2-octanol (**7a**) were similar to those of **5a** in that allylic silanes were formed in addition to the desired vinylsilanes. Thermolysis of *N*-phenylcarbamate **6c** at 125 °C for 1 h, followed by distillation and preparative GLC separation of the products, gave *trans*-1-trimethylsilyl-3-phenyl-1-propene (**13**) and *trans*-1-phenyl-3-trimethylsilyl-1-propene (**14**). The approximate

$PhCH_2CH(X)CH_2SiMe_3 \longrightarrow$

6a, X = OH
c, X = OC(S)NHPh

trans-$PhCH_2CH{=}CHSiMe_3$ (**13**, ~45%) + *trans*-$PhCH{=}CHCH_2SiMe_3$ (**14**, ~38%)

yields were 45 and 38%, respectively. The GLC analysis indicated that a third component was present in less than 10% yield, but it was not isolated and identified.

The Chugaev process applied to **7a** was effective in the sense that a 72% conversion to silicon-containing products occurred, but the elimination was not highly regioselective. The ratio of vinylsilane to allylsilane was somewhat variable in separate

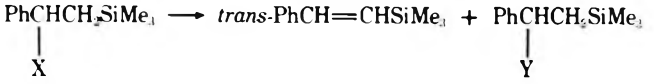
$CH_3(CH_2)_5CH(X)CH_2SiMe_3 \longrightarrow$

7a, X = OH
d, X = OC(S)SCH$_3$

trans-$CH_3(CH_2)_5CH{=}CHSiMe_3$ (**15**) + $CH_3(CH_2)_4CH{=}CHCH_2SiMe_3$ (**16**)

experiments and ranged from 2/1 to 3/1. The vinylsilane was identified as *trans*-1-trimethylsilyl-1-octene (**15**) on the basis of its NMR spectrum and analysis. The allylic silane could not be isolated, but its presence was inferred from the NMR spectrum of the product.

Application of ester thermolyses to the synthesis of β-styryltrimethylsilane was complicated by the formation of side products characteristic of ion-pair return processes. Thus, the *N*-phenylcarbamate **8b** on heating yielded, in addition to a 43% yield of the desired *trans*-1-phenyl-2-trimethylsilylethene (**17**), a 33% yield of *N*-(1-phenyl-2-trimethylsilylethyl)aniline



8a. X = OH	**17**	
b. X = OC(O)NHPh	43%	**18**. Y = NHPh, 33%
d. X = OC(S)SCH3		**19**. Y = SCH3, 25%

(**18**). The Chugaev procedure via **8d** gave no isolable quantities of **17**. The only product identified was the methyl thioether **19**, isolated in 25% yield.

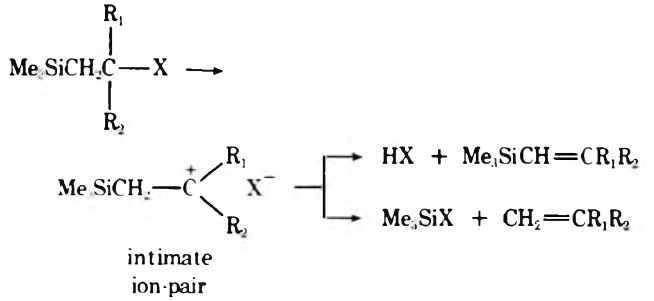
Discussion

The most significant observation in this study is that elimination reactions of esters of β-hydroxyalkyltrimethylsilanes can be controlled to proceed with complete C–SiMe3 cleavage or complete C–H cleavage simply by varying the leaving group. Elimination reactions involving C–SiMe3 cleavage of β-functional organosilanes, both polar and thermal four-center, are common and well documented.[2] Retention of silicon in the elimination product, over the range of substrates reported here, is without precedent. Syntheses of vinylsilanes in preparatively useful amounts can be accomplished by thermolysis of *N*-phenylcarbamates or *N*-phenylthiocarbamates if the elimination reaction can proceed in only one direction. This is best evidenced by the conversion of **1b** to **3** in 94% yield and **4c** to **9** in 72% yield.

Ester thermolysis is not a general route to vinylsilanes, however, because the reactions are not highly regioselective. When elimination can occur in more than one direction, mixtures of vinylsilane and allylic silane are produced. This limitation is most clearly seen in the case of esters of **5a** where the allylic silane **12** was the major product.

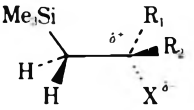
The reactions appear to be highly stereoselective, favoring the formation of trans vinylsilanes. This conclusion is only tentative, however, inasmuch as the analysis was by NMR on purified materials and small amounts of cis vinylsilanes, if formed, may have escaped detection.

In order to rationalize the dependence of vinylsilane vs. alkene formation on the leaving group, as is evident from the data in Table II, we envision as the critical step formation of an ion-pair intermediate. Deprotonation of the carbonium ion yields vinylsilane; desilylation yields alkene. The species acting as the base is either the anion of the leaving group or some species derived from the leaving group. For example, in thermolysis of *N*-phenylcarbamates the base could be either $PhNHCO_2^-$ or $PhNH^-$. Previous work in thermal elimination reactions of esters has established the importance of ion-pair



intermediates and has shown that it is the counterion (rather than an external base) which abstracts the proton from the carbonium ion.[13]

Developing cationic character at the carbon β to silicon will be facilitated by hyperconjugative electron release from the C(β)–Si bond in the transition state.[14] Hyperconjugative stabilization of this type is believed to be most effective when the trimethylsilyl group and the leaving group are anti to each other.[2a]



The ion pair generated from such a transition state will have the anion of the leaving group oriented at the opposite face of the R_1CR_2 plane from the trimethylsilyl group. If the anion is strongly basic, deprotonation will be fast relative to motion within the ion pair and vinylsilane will be formed. If the anion is more weakly basic, deprotonation will be slowed relative to rotation about the C(α)–C(β) bond, the trimethylsilyl group and the anion will be brought into closer proximity, and desilylation can occur. For the case of the methanesulfonate ester **1f**, decomposition under the conditions of its formation may proceed by attack by chloride ion at the trimethylsilyl group during the ionization process.[2b]

The poorer leaving groups examined in this study are also the more basic. The transition state for a poorer leaving group will appear later along the reaction coordinate, cationic character will be more highly developed, and the geometric requirement for carbon–silicon hyperconjugation more pronounced. This factor also favors vinylsilane formation relative to alkene formation.

While the above discussion was presented in the context of vinylsilane formation, exactly the same argument applies to allylsilane formation. Insufficient evidence is available to assess the factors which influence the vinylsilane to allylsilane ratio. The tendency for formation of one or the other is not particularly pronounced. Thermolysis of **6c** produces almost equal amounts of vinylsilane **13** and allylsilane **14**. Vinylsilane **15** predominates over allylsilane **16** by 2–3/1 on thermolysis of **7d**. The vinylsilane/allylsilane ratio from **5b** and **5d** was 1/7, but here the tendency for formation of double bonds endocyclic to six-membered rings seems to be the most important factor.

Support for the ion-pair mechanism can be found among several observations. The pattern of reactivity relative to substrate structure and leaving group ability parallels that observed in reactions which proceed through carbonium ion intermediates. The tertiary and sterically compressed[15] 2-trimethylsilylmethyl-2-adamantyl *N*-phenylthiocarbamate **1c** underwent spontaneous decomposition at 25 °C while the secondary *N*-phenylthiocarbamates **4c** and **6c** were stable enough to be isolated, and required temperatures of 125–140 °C to effect rapid elimination.

The side products **18** and **19** obtained from thermolysis of the benzylic esters **8b** and **8c** are typical nucleophilic substitution products associated with ion-pair return.

In agreement with its postulated involvement in stabilizing the transition state for ionization, the presence of a β-trimethylsilyl substituent exerts an accelerating effect on these ester thermolyses. The *N*-phenylcarbamates **1b**, **4b**, **5b**, and **8b** underwent smooth elimination at temperatures in the range 120–200 °C. Conditions for thermolysis of alkyl carbamate esters to alkenes are usually in the range 325–350 °C for kinetic studies in the gas phase[16] and 230–300 °C for preparative work in condensed phases.[17] Similarly, the *S*-methyl xanthate pyrolyses occurred at lower temperatures than those reported for Chugaev eliminations in the literature.[11]

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on JEOL PS-Fourier transform, Varian HA-100, and Hitachi Perkin-Elmer R-20 spectrometers in $CDCl_3$ or CCl_4 and chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Infrared spectra (ir) were obtained on a Perkin-Elmer 337 grating spectrophotometer as KBr disks for solids and pressed films for liquids and were calibrated with either the 1601- or the 907-cm^{-1} band of polystyrene. Melting points are corrected and were measured on a Thomas-Hoover apparatus. Boiling points are uncorrected. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionizing potential of 70 eV. Gas chromatography was carried out on a Varian Aerograph 90-P3 with a thermal conductivity detector. Peak areas were determined with a disc integrator.

Elemental microanalyses were performed by Alfred Bernhardt, Engelskirchen, West Germany, and by Atlantic Microlab, Inc., Atlanta, Ga.

All reactions involving air-sensitive compounds were carried out in an atmosphere of dry nitrogen. Tetrahydrofuran was distilled from calcium hydride and stored over molecular sieves 4A under argon or nitrogen. *n*-Butyllithium in *n*-hexane was purchased from Alfa Inorganics.

β-Hydroxyalkyltrimethylsilanes. The addition of trimethylsilylmethylmagnesium chloride to carbonyl compounds in tetrahydrofuran was performed as described by Peterson.[1b]

2-Trimethylsilylmethyl-2-adamantanol (1a) was obtained in 89% yield, mp 48–55 °C, and purified by recrystallization from absolute ethanol (mp 58.5–59.5 °C): ir (KBr) 3520, 3455, 1245, 855, and 837 cm^{-1}; NMR (CCl_4) δ 0.08 (s, 9, $SiMe_3$), 1.1 (s, 2, CH_2Si), and 1.5–2.2 (m, 14, ring H); mass spectrum *m/e* (rel intensity) 223 (13), 220 (10), 205 (35), 151 (15), 148 (63), 75 (100), and 73 (53).

Anal. Calcd for $C_{14}H_{26}OSi$: C, 70.52; H, 10.99; Si, 11.78. Found: C, 70.61; H, 10.94; Si, 11.53.

1-Trimethylsilyl-3,3-dimethyl-2-butanol (4a) was prepared by addition of the Grignard reagent prepared from 10.5 g (85 mmol) of chloromethyltrimethylsilane to 7.9 g (92 mmol) of pivaldehyde. After distilling at 26 °C (1 Torr), 10.34 g (73%) of **4a** was obtained: ir (thin film) 3505 (OH), 2955, 2900, 2870, 1248, 862, and 838 cm^{-1}; NMR (CCl_4) δ 0.07 (s, 9, $SiMe_3$), 0.68 and 0.73 (m, 2, CH_2SiMe_3, ABM system), 0.88 (s, 9, *t*-Bu), 1.3 (s, 1, OH), and 3.4 (d, d, J = 4, 10 Hz, 1, CHOH); mass spectrum *m/e* (rel intensity) 117 (44), 75 (60), 73 (100), 57 (26), and 41 (38).

Anal. Calcd for $C_9H_{22}OSi$: C, 62.00; H, 12.72; Si, 16.11. Found: C, 61.90; H, 12.63; Si, 15.92.

1-Trimethylsilylmethylcyclohexanol (5a). The addition of trimethylsilylmethylmagnesium chloride to cyclohexanone has been reported without details.[1b] We obtained **5a** in 86% yield after sublimation (mp 35–36.5 °C): ir (KBr) 3300, 1246, 864, and 838 cm^{-1}; NMR (CCl_4) δ 0.08 (s, 9, $SiMe_3$), 0.88 (s, 2, CH_2Si), 1.04 (s, 1, OH), and 1.4 [br s, $(CH_2)_5$]; mass spectrum *m/e* (rel intensity) 186 (5), 171 (3), 168 (3), 153 (3), 96 (10), 91 (27), 81 (26), 75 (90), 73 (100), and 54 (58).

1-Trimethylsilyl-3-phenyl-2-propanol (6a) was isolated in 35% yield after distillation: bp 62 °C (0.17 Torr); ir (neat) 3445 (m, OH), 1246 (s), 853 and 838 (s, $SiMe_3$), 743 (m), and 698 cm^{-1} (s); NMR ($CDCl_3$) δ 7.28 (s, 5, aromatic), 4.0 (m, 1, CHO), 2.8 (m, 2, AB part of ABM system, $PhCH_2$), 1.63 (s, 1, OH), 0.98 (d, 2, J = 14 Hz, CH_2Si), and 0.17 (s, 9, $SiMe_3$); mass spectrum *m/e* (rel intensity) 208 (<1), 190 (1), 189 (1), 175 (1), 119 (5), 118 (13), 117 (56), 92 (19), 91 (20), 75 (54), 74 (12), and 73 (100).

Anal. Calcd for $C_{12}H_{20}OSi$: C, 69.17; H, 9.67; Si, 13.48. Found: C, 69.41; H, 9.78; Si, 13.49.

1-Trimethylsilyl-2-octanol (7a) was isolated in 80% yield after distillation at atmospheric pressure (bp 156–168 °C): ir (neat) 3360, 2960, 2930, 2860, 1248, 858, and 836 cm^{-1}; NMR (CCl_4) δ 0.0 (s, 9, Me_3Si), 0.5–1 (m, 5, CH_3 and CH_2Si), 1–1.5 (m, 10, CH_2), 1.6 (s, 1, OH), and 3.4–3.7 (m, 1, CHOH); mass spectrum *m/e* (rel intensity) 189 (4), 169 (4), 147 (4), 118 (8), 117 (73), 75 (97), and 73 (100).

Anal. Calcd for $C_{11}H_{26}OSi$: C, 65.27; H, 12.95; Si, 13.88. Found: C, 65.20; H, 12.72; Si, 13.85.

1-Phenyl-2-trimethylsilylethanol (8a) has been described by Hauser and Hance[1b] (bp 103–104 °C, 3 Torr). The material we obtained crystallized on standing, mp 27.5–29.5 °C.

Reaction of 2-Trimethylsilylmethyl-2-adamantanol (1a) with Methanesulfonyl Chloride. A solution containing 2.0 g (8.4 mmol) of **1a** in 30 ml of purified tetrahydrofuran was cooled to −30 °C and 8.4 mmol (4.2 ml of a 2.0 M solution in *n*-hexane) of *n*-butyllithium was added. After 10 min, 0.97 g (8.4 mmol) of methanesulfonyl chloride was added via syringe and the solution stirred at 25 °C for 12 h. The reaction mixture was diluted with 60 ml of ether, washed with three 50-ml portions of saturated ammonium chloride solution, and dried over magnesium sulfate. Evaporation of the solvent left 1.44 g of crude product which was examined by NMR. No vinylsilane was present. The product was taken up in 5 ml of pentane, passed through a short column of neutral alumina, and the column washed with 50 ml of pentane. The pentane was evaporated to leave 1.14 g (91%) of methyleneadamantane (**2**), mp 134–136 °C (lit. 135.8–136.5 °C),[18] identified further by comparing its NMR spectrum with that reported.

Isolation of 2-(Trimethylsilylmethylene)adamantane (3) from Chugaev Reaction of 1a. A solution of 7.25 g (0.03 mol) of **1a** in 50 ml of tetrahydrofuran was cooled to −5 °C and treated successively with 13.2 ml (0.03 mol) of *n*-butyllithium in *n*-hexane and 11.55 g (0.15 mol) of carbon disulfide. After stirring at 25 °C for 4 h, the solution was cooled to −5 °C and 8.6 g (0.06 mol) of iodomethane added. The solution was then stirred at 25 °C for 1.5 h. The solvent was evaporated and the residue partitioned between 100 ml of ether and 100 ml of saturated ammonium chloride solution. The aqueous layer was extracted with 100 ml of ether and the combined ether solutions dried ($MgSO_4$) and evaporated. The residue was chromatographed on 88 g of silica gel (column prepared in *n*-pentane) and eluted with 240 ml of *n*-pentane to afford 5.39 g of product identified by NMR as a 3:1 mixture of 2-(trimethylsilylmethylene)adamantane (**3**) and methyleneadamantane (**2**). The composition was determined by integration of the respective vinyl proton signals of **3** (δ 4.96) and **2** (δ 4.48).

A portion (2.93 g) of the mixture was purified by chromatography on a column prepared from 50 g of silica gel, 12 g of silver nitrate, and 2.5 g of Celite.[19] Elution with dichloromethane gave 1.57 g (44%) of **3** as a colorless liquid: ir (neat) 3040 (w, vinyl C–H), 2955 (sh), 2910, 2855, 1620, 1245, 895, 861, and 841 cm^{-1}; NMR (CCl_4) δ 0.13 (s, 9, Me_3Si), 1.9 (br s, 12, ring H), 2.2–2.8 (m, 2, allylic H), and 4.96 (s, 1, vinyl H); mass spectrum *m/e* (rel intensity) 221 (6), 220 (17), 206 (23), 205 (100), 73 (17), and 59 (24).

Anal. Calcd for $C_{14}H_{24}Si$: C, 76.28; H, 10.97; Si, 12.74. Found: C, 76.34; H, 10.86; Si, 12.54.

Reaction of 1a with Phenyl Isothiocyanate. 2-Trimethysilylmethyl-2-adamantanol (**1a**, 3.1 g, 13 mmol) dissolved in 80 ml of dry tetrahydrofuran was cooled to −30 °C under an atmosphere of nitrogen. Then 7.2 ml (13 mmol) of a 1.8 M solution of *n*-butyllithium in *n*-hexane was added slowly keeping the temperature at or below −30 °C. The solution was stirred for 40 min before phenyl isothiocyanate (1.7 g, 13 mmol) was added slowly. The reaction mixture stood for 22 h at room temperature. Workup was carried out by adding 100 ml of dichloromethane and then extracting the dichloromethane solution twice with 100-ml portions of saturated ammonium chloride. After drying ($MgSO_4$) the solvent was removed on a rotary evaporator to leave 4.1 g of crude product. This was subjected to dry column chromatography on silica gel using a mixture of hexanes as solvent. There was obtained from the highest R_f band (0.6–1.0) 2.1 g (73%) of vinylsilane **3** which was analyzed by GLC to be 95% pure. The only impurity apparent in the GC analysis and by NMR was methyleneadamantane (**2**).

Preparation of 2-Trimethylsilylmethyl-2-adamantyl *N*-Phenylcarbamate (1b). In the same manner, 10.0 g (42 mmol) of **1a** was converted to its alkoxide with *n*-butyllithium and allowed to react with 5.0 g (42 mmol) of phenyl isocyanate. The crude product, a solid (15.6 g), was recrystallized from a dichloromethane–n-hexane (1:5) solution to give 11.7 g (78%) of **1b**, mp 140.5–142 °C dec. The analytical sample was obtained by recrystallization from ether: mp 154.5–155 °C dec; ir (KBr) 3330 (s, NH), 1695 (s, C=O) and 859 cm^{-1} (m, $SiMe_3$); NMR ($CDCl_3$) δ 7.03–7.39 (m, 5, aromatic), 6.49 (br, 1, NH), 1.58–2.56 (br m, 14, adamantyl), 1.75 (s, 2, $-CH_2SiMe_3$), and 0.09 (s, 9, $SiMe_3$).

Anal. Calcd for $C_{21}H_{31}NO_2Si$: C, 70.54; H, 8.74; N, 3.92; Si, 7.85. Found: C, 70.47; H, 8.67; N, 4.04; Si, 7.92.

Thermolysis of 1b. A 100-ml round-bottom flask fitted with a short-path distillation head and containing 7.1 g (19.9 mmol) of **1b** was placed in an oil bath preheated to 165 °C. Gas was evolved as the ester melted. The resulting liquid was distilled (0.1 Torr) to give 6.1 g of a clear, colorless mixture of two liquids. The distillate was taken up in *n*-pentane (50 ml), extracted with three 50-ml portions of 2 N HCl, washed with 50 ml of water, and dried ($MgSO_4$). The pentane was evaporated to leave 4.1 g (94%) of vinylsilane **3**, the NMR of which was identical with that of the analytical sample described above, except for the presence of a trace of pentane as the only impurity.

Reaction of 1a with Burgess' Reagent. Analysis by Gas Chromatography. To a solution containing 200 mg (0.84 mmol) of (carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester[12] in 20 ml of toluene at reflux was added 153 mg (0.64 mmol) of **1a** in 3 ml of toluene. After 16 h at reflux, the reaction mixture was

cooled and extracted with two 10-ml portions of saturated ammonium chloride. Analysis of the product was carried out using a 10 ft × 0.25 in. 20% SE-30 on Chromosorb W column at 178 °C at a helium flow rate of 40 ml/min. Cyclododecene was added as an internal standard and the areas of the peaks corrected by calibration with known mixtures. The analytical yields determined by three separate experiments were vinylsilane **3**, 39% and methyleneadamantane **2**, 51%.

Analysis of Chugaev Reaction of 1a by Gas Chromatography. The reaction was carried out as described previously but on a smaller scale (0.64 mmol) and analyzed as in the preceding experiment. The analytical yields were vinylsilane **3**, 70%, and methyleneadamantane **2**, 28%.

Preparation of 1-Trimethylsilyl-3,3-dimethyl-2-butyl *N*-Phenylcarbamate (4b). Conversion of 9.1 g (52 mmol) of **4a** to its *N*-phenylcarbamate was carried out as described previously for the synthesis of **1b** from **1a**. The crude product (15.5 g) was recrystallized from ether–pentane (1:5) to give 11.6 g (76%) of **4b**: mp 75.5–77.5 °C; ir (KBr) 3410 (NH), 1720 (C=O), 1535, 1450, 1370, 1320, 1250, 1230, 1220, 1069, 950, 858, 840. 750, and 690 cm^{-1}; NMR ($CDCl_3$) δ 0.07 (s, 9, $SiMe_3$), 0.84 (d, 2, J = 6 Hz, CH_2SiMe_3), 0.94 (s, 9, t-Bu), 4.88 (d, d, 1, CH), 6.54 (br, 1, NH), and 6.96–7.52 (m, 5, aromatic).

Anal. Calcd for $C_{16}H_{27}NO_2Si$: C, 65.48; H, 9.27; N, 4.77; Si, 9.57. Found: C, 65.50; H, 9.18: N, 4.82; Si, 9.83.

1-Trimethylsilyl-3,3-dimethyl-2-butyl *N*-phenylthiocarbamate (4c) was prepared in a similar manner from **4a** using phenyl isothiocyanate. The purified material, mp 117–118 °C, was obtained in 79% yield after recrystallization from *n*-pentane: ir (KBr) 3180 (NH), 2970, 1530, 1390, 1246, 1224, 1204, 1172, 1151, 1061, 1016, 863, 836, 740, and 693 cm^{-1}; NMR ($CDCl_3$) δ 0.13 (s, 9, $SiMe_3$), 1.0 (s, 9, t-Bu), 0.9–1.12 (m, 2, CH_2SiMe_3), 5.71 (d, d, 1, CHO), 7.04–7.47 (br, 5, arom), 8.35–8.9 (br, 1, NH). The analytical sample was obtained by further recrystallization from *n*-pentane, mp 118.5–119.5 °C dec.

Anal. Calcd for $C_{16}H_{27}NOSSi$: C, 62.08; H, 8.79; N, 4.52; S, 10.36; Si, 9.07. Found: C, 62.31; H, 8.94; N, 4.51; S, 10.53; Si, 9.24.

Thermolysis of 4c. A 25-ml round-bottom flask fitted with a short path distillation head and containing 6.42 g (20.7 mmol) of **4c** was heated (oil bath) while cooling the distillation receiver in an ice–salt bath. Decomposition occurred on melting (bath temperature 120 °C). The temperature was maintained at 120 °C for 20 min, then the temperature increased to 140 °C and vacuum applied to the system resulting in the distillation of a clear, colorless liquid containing two phases. The distillate was taken up in 100 ml of pentane and extracted with two 25-ml portions of 2 N hydrochloric acid followed by 25 ml of water. The pentane was removed by distilling through a Vigreux column and the product purified by distillation at atmospheric pressure. The yield of *trans*-1-trimethylsilyl-3,3-dimethyl-1-butene (**9**) was 2.32 g (72%), bp 132–134 °C (reported bp 128–130 °C). The ir, NMR, and mass spectra corresponded to those reported.[10f,20]

Thermolysis of 4b was slow even at 200 °C. After 30 h 11.61 g (40 mmol) of **4b** gave 1.73 g (28%) of **9** along with 15% of *N,N'*-diphenylurea (1.32 g).

Preparation and Thermolysis of 1-Trimethylsilylmethyl-1-cyclohexyl *N*-Phenylcarbamate (5b). The *N*-phenylcarbamate was prepared from 6.6 g (35 mmol) of **5a** and phenyl isocyanate exactly as described previously for the preparation of **1b**. The crude product (11.4 g) was recrystallized from pentane to give 5.3 g (49%) of **5b**: mp 81–82 °C; ir (KBr) 3305 (s, NH), 1690 (s, C=O), 1234 (s, C–O), and 842 cm^{-1} (m, $SiMe_3$); NMR ($CDCl_3$) δ 7.12–7.59 (m, 5, aromatic), 6.62 (br, 1, NH), 1.32–2.60 (br, 12, cyclohexyl and $-CH_2Si$), and 0.16 (s, 9, $SiMe_3$).

Anal. Calcd for $C_{17}H_{27}NO_2Si$: C, 66.84; H, 8.91; N, 4.58; Si, 9.19. Found: C, 66.82; H, 8.97; N, 4.73; Si, 9.35.

Thermal decomposition of 5.02 g (16.4 mmol) of **5b** was carried out as described for **1b**. The bath temperature was 113–125 °C. After distillation at 0.05 Torr and extraction with ether and 2 N HCl, 2.58 g (93%) of a mixture of **11** and **12** was obtained. Analysis of the mixture by NMR was performed by integration of their respective trimethylsilyl signals. The NMR spectrum of **11** has been reported.[10d] Characterization of **12** is described below. The ratio **11**/**12** was 13/87.

Characterization of 1-Trimethylsilylmethylcyclohexene (12). Methyl(carboxylsulfamoyl)triethylammonium hydroxide inner salt[12] (3.57 g, 15 mmol) was dissolved in 60 ml of dichloromethane and added to an ice-cooled solution of 2.64 g (14.1 mmol) of **5a** in 30 ml of dichloromethane. The solution was allowed to warm to room temperature for 5 min, extracted with two 100-ml portions of water, and dried over magnesium sulfate. Evaporation of the solvent left 4.57 g of a mixture containing a liquid and a solid. The liquid (1.28 g) was removed by pipet and determined to be a 3:2 mixture of **12** and methylenecyclohexane (**10**) by NMR. Preparative GLC separation on a 10-ft 20% Silicone Fluoro QF-1 column at 166 °C afforded a pure sample of **12**: ir (neat) 2940, 2860, 2845, 1245, 1170, 920, 860, 845, and 695 cm^{-1}; NMR (CCl_4) δ 0.05 (s, 9, $SiMe_3$), 1.38 (br s, 2, $SiCH_2$), 1.4–2.1 (m, 8, ring protons), 5.15 (br s, 1, vinyl H); mass spectrum *m/e* 168, 73 (base peak).

Anal. Calcd for $C_{10}H_{20}Si$: C, 71.34; H, 11.97; Si, 16.68. Found: C, 71.31; H, 11.94; Si, 16.90.

Chugaev Reaction of 1-Trimethylsilylmethyl-1-cyclohexanol (5a). The procedure followed was similar to that used for **1a**. The experiment was carried out on 7.2 g (38.5 mmol) of **5a**. The crude product was heated at 160 °C (oil bath) for 30 min and separated by dry column chromatography on 350 g of silica gel. There was obtained 4.08 g (63%) of material (R_f 0.6–1.0) analyzed by NMR to be a mixture of **11** (13%) and **12** (87%).

The vinylsilane **11** was isolated from the mixture by the following procedure which is based on its much slower rate of epoxidation than the allylsilane **12**. A sample (0.314 g, 1.87 mmol) of the product was treated with 0.378 g (1.87 mmol) of 85% *m*-chloroperoxybenzoic acid in 12 ml of dichloromethane at −14 to −24 °C for 12 h. The solution was extracted with four 10-ml portions of saturated sodium bicarbonate, then with 10 ml of brine and dried ($MgSO_4$). The crude product (0.289 g) was subjected to preparative GLC on a 10-ft 20% SE-30 column at 158 °C. Three peaks were collected having retention times of 5.5, 7.7, and 9.2 min. The product with the longest retention time was identified as **11** by comparing its NMR and ir spectra with those reported.[10d] The products with retention times of 5.5 and 7.7 min are 2-methylenecyclohexanol and its corresponding trimethylsilyl ether formed by epoxidation and cleavage of **12**.

Preparation and Thermolysis of 1-Trimethylsilyl-3-phenyl-2-propyl *N*-Phenylthiocarbamate (6c). The preparation of ester **6c** from 5.0 g (24 mmol) of **6a** and phenyl isothiocyanate was similar to those described previously. The crude product (9.9 g) was recrystallized from a mixture of ether and pentane (1:10) to give 6.1 g of **6c** as off-white crystals, mp 103.5–104.5 °C. The analytical sample was obtained from an additional recrystallization from diethyl ether–*n*-pentane (1:10) as fine white needles: mp 105.5–106 °C; ir (KBr) 3210 (m, NH), 1545 (s), 1214 (s), 1168 (s), 1021 (s), 852 and 836 (m, $SiMe_3$), and 738 cm^{-1} (s); NMR ($CDCl_3$) δ 8.61–8.30 (br, 1 NH), 7.27 (s, 10, aromatic), 5.95 (m, 1, $-CH_2O$), 3.11 (m, 2, $PhCH_2-$), 1.19 (m, 2, $-CH_2Si$), and 0.14 (s, 9, $SiMe_3$).

Anal. Calcd for $C_{19}H_{25}NOSSI$: C, 66.42; H, 7.33; N, 4.08; S, 9.33; Si, 8.17. Found: C, 66.56; H, 7.45; N, 4.05; S, 9.15; Si, 8.09.

The thiocarbamate **6c** (5.8 g, 17 mmol) was placed in a 25-ml round-bottom flask which was then fitted with a reflux condenser and a drying tube. The flask was heated to 125 °C for 1 h. The reaction mixture was worked up by adding 50 ml of *n*-pentane and extracting with two 50-ml portions of 2 N hydrochloric acid followed by one 50-ml portion of water. The pentane layer was dried ($MgSO_4$) and evaporated to leave 3.5 g of crude product. The crude product was vacuum distilled and the fraction of bp 49–53 °C (0.13 Torr) collected, 2.7 g (84%). This fraction was determined to be a mixture of three components with retention times of 7.0, 7.9, and 9.5 min in the ratio 50:8:42, respectively, by analytical GLC at 170 °C on a 10-ft 20% SE-30 on Chromosorb W column. Preparative GLC at 135 ° was performed and the two major components collected. The product with the shortest retention time was the vinylsilane **13**: ir (neat) 1619 (w), 1608 (w), 1247 (s), 990 (m), 864 (s), 837 (s), and 696 cm^{-1} (s); NMR ($CDCl_3$) δ 7.16 (br s, 5, aromatic), 6.05 (doublet of triplets, 1, J = 4.8 and 16.0 Hz. $PhCH_2CH=$), 5.70 (d, 1, J = 16.0 Hz, $=CHSi$), 3.41 (d, 2, J = 4.8 Hz. $PhCH_2-$), and 0.07 (s, 9, $SiMe_3$); mass spectrum *m/e* (rel intensity) 190 (15), 175 (23), 117 (7), 116 (7), 115 (11), 93 (15), 91 (4), 77 (11), 75 (10), 74 (11), 73 (100), 65 (14), 59 (43), 45 (18), and 43 (15).

Anal. Calcd for $C_{12}H_{18}Si$: C, 75.72; H, 9.53; Si, 14.75. Found: C, 75.52; H, 9.41; Si, 14.64.

The product with the longest retention time was the allylsilane **14**, identified by comparing its ir, NMR, and mass spectra with those reported in the literature.[21]

Preparation and Thermolysis of 1-Trimethylsilyl-2-octyl *S*-Methyl Xanthate (7d). The procedure employed was similar to that used for **1a** except that in this case the xanthate was sufficiently stable to be isolated as a light yellow liquid. From 5.00 g (24.8 mmol) of **7a** was obtained 6.91 g (95%) of **7d**: NMR (CCl_4) δ 0.10 (s, 9, $SiMe_3$), 0.5–2 (m, 15), 2.58 (s, 3, SCH_3), 5.5–5.9 (m, 1, CHO).

Elimination occurred on distilling through a short-path apparatus (bath temperature 216 °C) to give 3.29 g (72%) of product. This material was predominantly *trans*-1-trimethylsilyl-1-octene (**15**) as evidenced by its 100-MHz NMR spectrum, which exhibited signals for the vinyl protons consistent with this structure. The vinyl H at C(1) appeared as a doublet (J = 18 Hz) at δ 5.5 and the vinyl proton at C(2) appeared as a doublet of triplets (J = 18, 6 Hz) at δ 5.95. An additional multiplet at δ 5.25 was present corresponding to a smaller,

but undetermined, amount of an impurity presumed to be 1-trimethylsilyl-2-octene (**16**).[22]

A pure sample of **15** was obtained by treating 15.7 g of a similar reaction mixture with 17.4 g of *m*-chloroperoxybenzoic acid in dichloromethane (180 ml) for 11 h. Workup and distillation at 0.01 Torr afforded 3.0 g of a fraction (bp 30–37 °C) which by NMR was cleanly **15**: NMR (CCl_4) δ 0.16 (s, 9, $SiMe_3$), 0.6–1.6 (m, 11, C_5H_{11}), 2.1 (m, 2, CH_2C=), 5.6 (d, 1, J = 18 Hz, =C**H**SiMe$_3$), 6.0 (d, t, 1, J = 18, 6 Hz, **H**C=CHSiMe$_3$).

Anal. Calcd for $C_{11}H_{24}Si$: C, 71.65; H, 13.12; Si, 15.23. Found: C, 71.54; H, 13.14; Si, 15.15.

Preparation and Thermolysis of 1-Phenyl-2-trimethylsilylethyl *N*-Phenylcarbamate (8b). By the usual procedure 15.2 g (78 mmol) of **8a** was converted to its *N*-phenylcarbamate. The crude product (25.4 g) was recrystallized from absolute ethanol to afford 11.3 g (46%) of **8b**: mp 89.5–90.5 °C; ir (KBr) 3270 (s, NH), 1690 (s, C=O), 1309 (s, C–N), 1240 (s br, C–O), 876 (s, $SiMe_3$), and 849 cm^{-1} (s, $SiMe_3$); NMR ($CDCl_3$) δ 6.91–7.47 (m, 10, aromatic), 6.60 (br, 1, NH), 5.84 (doublet of doublets, 1, J = 7.0 and 8.4 Hz, methine), 1.37 (d, 1, J = 7.0 Hz) and 1.33 (d, 1, J = 8.4 Hz) (both methylene), and −0.10 (s, 9, $SiMe_3$).

Anal. Calcd for $C_{18}H_{23}NO_2Si$: C, 68.97; H, 7.40; N, 4.47; Si, 8.96. Found: C, 68.89; H, 7.52; N, 4.53; Si, 8.94.

A flask containing 11.16 (35.6 mmol) of **8b** was placed in an oil bath preheated to 197 °C. The carbamate melted rapidly with gas evolution. After heating for 15 min the resulting liquid was cooled and filtered (removing 0.18 g of *N,N'*-diphenylurea) and washed with 20 ml of 2 N HCl. Addition of the hydrochloric acid caused the precipitation of a large amount of white hydrochloride salt. This was removed by filtration, dried under vacuum, then shaken vigorously with 150 ml of 20% sodium hydroxide and 200 ml of diethyl ether. The ether layer was washed with 100 ml of water, dried ($MgSO_4$), and evaporated to give 3.2 g (33%) of 1-phenyl-*N*-phenyl-2-trimethylsilylethylamine (**18**) as a white solid, mp 56–58 °C. The analytical sample was recrystallized from diethyl ether–*n*-pentane: mp 58–59 °C; ir (KBr) 3420 (s, NH), 1602 (s), 1505 (s), 1320 (s, C–N), 1246 (s), 868 (s, $SiMe_3$), 846 (s, $SiMe_3$), 750 (s), 704 (s), and 693 cm^{-1} (s); NMR ($CDCl_3$) δ 6.38–7.43 (m, 10, aromatic), 4.44 (t, 1, J = 7.0 Hz, PhC**H**N), 4.00 (br, 1, NH), 1.19 (d, 2, J = 7.0 Hz, –C**H**$_2$SiMe$_3$), and 0.01 (s, 9, $SiMe_3$); mass spectrum *m/e* (rel intensity) 269 (11), 182 (12), 177 (22), 165 (14), 150 (25), 104 (11), 93 (14), and 73 (100).

Anal. Calcd for $C_{17}H_{23}NSi$: C, 75.78; H, 8.60; N, 5.20; Si, 10.42. Found: C, 75.82; H, 8.63; N, 5.15; Si, 10.36.

The ether solution of that portion of the thermolysis product which did not dissolve in the 2 N hydrochloric acid and which was not precipitated as the hydrochloride salt was extracted once more with 10 ml of 2 N hydrochloric acid to ensure that all of the amines had been removed. The ether solution was washed with 10 ml of water, dried ($MgSO_4$), and the ether removed by distillation at atmospheric pressure. The residue was distilled and 2.7 g (43%) of *trans*-β-trimethylsilylstyrene (**17**) was collected, bp 45–46 °C (0.25 Torr) [lit. 80–83 °C (3 Torr),[10b] 98 °C (10.5 Torr)[23]]; the ir[10b] and NMR[10f] corresponded to those reported.

Chugaev Reaction Applied to 8a. When the Chugaev process was carried out on 10.5 g (50 mmol) of **8a** according to the usual procedure and the crude residue distilled at 0.005 Torr, 2.6 g of a fraction, bp 56–61 °C, was obtained. This fraction was identified as 1-methylthio-1-phenyl-2-trimethylsilylethane (**19**) and was obtained in a 25% yield: ir (neat) 3045 (w), 2970 (m), 2930 (m), 1730 (w), 1610 (w), 1500 (w), 1460 (m), 1248 (s), 1132 (br w), 861, (s, $SiMe_3$), 850 (sh s, $SiMe_3$), 726 (m), 720 (m), 710 (m), and 699 cm^{-1} (s); NMR ($CDCl_3$) δ 7.39 (br s, 5, aromatic), 3.90 (t, 1, J = 8.2 Hz, C**H**SCH$_3$), 1.95 (s, 3, –SCH$_3$), 1.39 (d, 2, J = 8.2 Hz, –C**H**$_2$SiMe$_3$), and 0.16 (s, 9, $SiMe_3$).

Anal. Calcd for $C_{12}H_{20}SSi$: C, 64.21; H, 8.98; S, 14.29; Si, 12.52. Found: C, 64.27; H, 8.74; S, 14.10; Si, 12.32.

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Registry No.—**1a**, 58540-98-0; **1b**, 58540-99-1; **1c**, 58541-00-7; **1d**, 58541-01-8; **1e**, 58541-02-9; **1f**, 58541-03-0; **3**, 58541-04-1; **4a**, 58541-05-2; **4b**, 58541-06-3; **4c**, 58541-07-4; **5a**, 55287-96-2; **5b**, 58541-08-5; **6a**, 58541-09-6; **6c**, 58541-10-9; **7a**, 58541-11-0; **7d**, 58541-12-1; **8a**, 17993-97-4; **8b**, 58541-13-2; **12**, 58541-14-3; **13**, 58541-15-4; **15**, 57365-47-6; **18**, 58541-16-5; **19**, 58541-17-6; methanesulfonyl chloride, 124-63-0; phenyl isothiocyanate, 103-72-0.

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Addition of Halogens to Vinylcylopropanes

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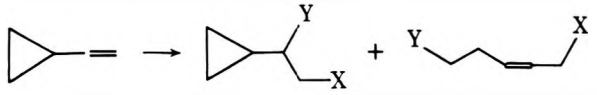
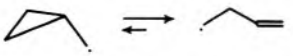
The halogenation of vinylcyclopropane (1) and 2-cyclopropylpropene (4) with chlorine, bromine, methyl hypochlorite (CH_3OCl), iodobenzene dichloride (IBD), and trichloroamine (NCl_3) is reported. A comparison of the product distribution from these halogenating reagents with 1 and 4 under ionic and radical conditions is used to distinguish between radical or cationic intermediates in these reactions. Chlorine, bromine, and NCl_3 react with 4 by an ionic process while IBD reacts primarily by a radical process. When 4 is treated with CH_3OCl the reaction proceeds by an ionic or radical mechanism depending on the reaction conditions. Apparently these reagents tend to react with vinylcyclopropanes by an ionic process because a very stable cyclopropylcarbinyl cation intermediate can be formed.

The addition of electrophiles[1] and radical addends[2] to vinylcyclopropanes is an area of current interest. It has been demonstrated that reactions which proceed through cyclopropylcarbinyl cation intermediates[1f] give predominantly cyclopropyl products under conditions of kinetic control.[1c,3]



When product formation is reversible, equilibration leads to formation of the thermodynamically more stable homoallyl isomer owing to relief of strain energy in the cyclopropane ring.[1c] Radical additions to vinylcyclopropanes proceed through classical cyclopropylcarbinyl and homoallyl intermediates.[2,4] Since at equilibrium the homoallyl radical is favored over the cyclopropylcarbinyl radical,[2c,4] a decrease in

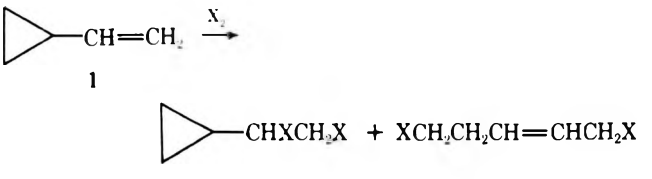


the concentration of the radical chain transfer agent will cause an increase in the amount of ring-opened products. These criteria have been used to confirm the presence of radical intermediates in the cyclopropylcarbinyl system.[2b]

In this study we investigated the halogenations of vinylcyclopropane (1) and 2-cyclopropylpropene (4) with chlorine, bromine, methyl hypochlorite, iodobenzene dichloride (IBD), and trichloroamine (NCl_3). It seemed to us that a comparison of the product distribution from the reaction of these halogenating reagents with 1 and 4 under various conditions would provide information about the intermediates in these reactions. A survey of the literature reveals that halogenation of vinylcyclopropanes has not been investigated thoroughly; only a product[1f] and kinetic[1a] study have appeared for the bromination of 1 under ionic conditions. The chlorinations of 1 and 4 have not been reported. Chlorine,[5] bromine,[5] and iodobenzene dichloride[6] are known to react by an ionic or radical process under the appropriate reaction conditions. Alkyl hypochlorites react with olefins by an ionic process in protic solvents.[7] The literature contains no unequivocal evidence for an ionic addition of alkyl hypochlorites to olefins in aprotic solvents.[7b,8] A radical process is involved when trichloroamine is treated with olefins[9a] and dienes.[9b] There is one reported case of an ionic process participating in the reaction of NCl_3 with olefins[9a] when a stable cation is formed.

Results and Discussion

In 1952 Slobodin[1e] reported that bromination of vinylcyclopropane 1 gave products **2a** and **3a** in a ratio of 3:2, respectively. During our investigation of the halogenations of vinycyclopropanes we found the product ratio for the bromination of 1 to be 6:1 by NMR analysis (Table I).[10,11] When 1 was treated with chlorine a similar ratio of products was observed.[12] This large preference for the 1,2 products is consistent with a cyclopropylcarbinyl cation[1c,3] intermediate and is in agreement with the open-cation intermediate proposed by Tidwell and Yates[1a] for the bromination of **1**.



a, X = Br
b, X = Cl

Bromination of 4 gives 1,2 and 1,5 products, while the chlorination of 4 gives substitution and 1,2 products but no 1,5 products.[13] The substitution products, 8 and **9**, in the chlorination of 4 are also consistent with an ionic but not a radical mechanism since formation of these products via a radical intermediate would involve transfer of a hydrogen atom. It appears that product **10** is formed by addition of HCl to 4 since direct treatment of 4 with HCl under the reaction conditions resulted in rapid formation of **10**.

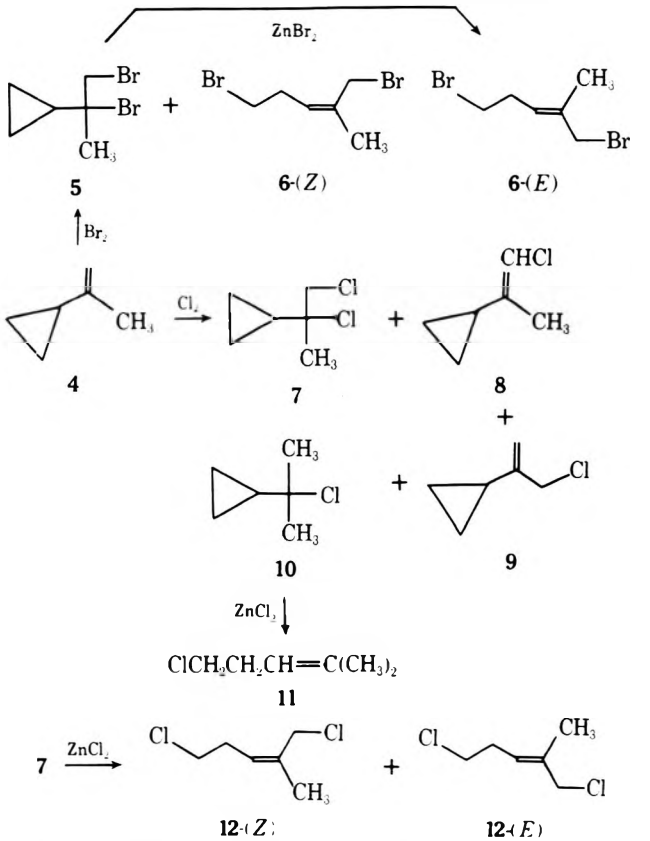


Table I. Halogenation of Vinylcyclopropanes 1 and 4

Run	Solvent	Mole fraction 1 or 4	Reaction[a] conditions	Halogenating reagent[b]	Percent products[c] From 1 2	From 1 3	From 4 5 or 7	From 4 6 or 12	From 4 8	From 4 9	From 4 10
1	C_5H_{12}	0.020	O_2, dark	Br_2	91	9	84	16			
2	CCl_4	0.020	O_2, dark	Br_2	86	14	83	17			
3	CH_2Cl_2	0.020	O_2, dark	Br_2	89	11	83	17			
4	Ether	0.094[d]		Br_2	86	14					
5	CCl_4	0.020	N_2, uv	Br_2			85	15			
6	CCl_4	0.500	N_2, uv	Cl_2			34		16	28	22
7	C_5H_{12}	0.020	O_2, dark	Cl_2	91[e]	9	33		14	47	6
8	CCl_4	0.020	O_2, dark	Cl_2			33		13	38	16
9	CH_2Cl_2	0.020	O_2, dark	Cl_2	90[e]	10	32		19	21	28
10	CH_2Cl_2	0.006[f]	O_2, dark	IBD			44	32	9	7	8
11	CH_2Cl_2	0.035[f]	N_2, uv	IBD			52	48			
12	CH_2Cl_2	0.012[f]	N_2, uv	IBD			43	57			
13	CH_2Cl_2	0.006[f]	N_2, uv	IBD			34	66			
14	CH_2Cl_2	0.003[f]	N_2, uv	IBD			28	72			
15	CH_2Cl_2	1.5×10^{-3} [f]	N_2, uv	IBD			24	76			
16	CH_2Cl_2	7.5×10^{-4} [f]	N_2, uv	IBD			20	80			
17	CH_2Cl_2	0.020	O_2, dark	NCl_3			52		20	28	
18	CCl_4	0.020	O_2, dark	NCl_3			50		18	32	
19	CCl_4	0.050	N_2, uv	NCl_3			50		22	28	
20		Neat	N_2, uv	NCl_3			46		20	34	

[a] The uv light was from a 275-W General Electric sunlamp. [b] Vinylcyclopropanes 1 and 4 were used in excess (ca. 10–40%). Neat bromine was added to the reaction mixture at −15 °C. A slow stream of N_2 or O_2 was used as a carrier gas to transport Cl_2 into the reaction mixture at −15 °C. A 6.0 M solution of 4 in CH_2Cl_2 was added to IBD dissolved in CH_2Cl_2 at 25 °C. NCl_3 was added dropwise as a 0.34 M solution in CCl_4 or CH_2Cl_2. [c] Product composition was determined by NMR analysis on an average of at least three runs. [d] Conditions under which Slobodin carried out the bromination of 1; see ref 1e. [e] Similar ratios were obtained by VPC. See ref 20. [f] Mole fraction IBD in CH_2Cl_2.

The data in Table I show that when 4 is treated with chlorine under ionic conditions (low mole fraction olefin, O_2 as an inhibitor, dark) or radical conditions (high mole fraction olefin, O_2 removed by N_2, and ultraviolet illumination) there is little change in the product distribution. This suggests that a radical intermediate is not involved in the chlorination of vinylcyclopropanes. Apparently the radical pathway does not compete effectively when chlorine is treated with vinylcyclopropanes because a very stable cyclopropylcarbinyl cation intermediate is formed.

Therefore, we turned our attention to halogenating reagents that might be more likely to react with vinylcyclopropanes by a radical mechanism. When 4 is treated with methyl hypochlorite under ionic conditions, in methylene chloride, products 7, 8, 9, and 13 are formed in a slow reaction. This appears to be the first reported case of an ionic process for the reaction of methyl hypochlorite with olefins in an aprotic solvent. Apparently the ionic process is competitive because a very stable cyclopropylcarbinyl cation intermediate can be formed. However, when the reaction is carried out under radical conditions a fast reaction gives only anti-Markownikoff products

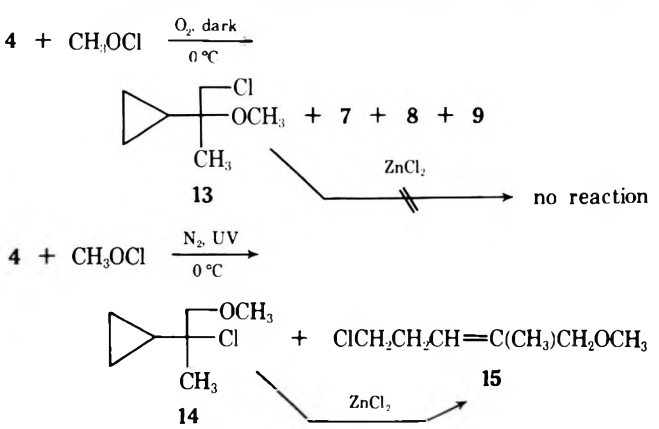


Table II. Reaction[a] of Methyl Hypochlorite with Vinylcyclopropane 4 under Radical Conditions at 0 °C

Mole fraction in CH_2Cl_2 CH_3OCl[b]	Mole fraction in CH_2Cl_2 4	Product composition 14	Product composition 15
0.08	Neat	100	
0.03	0.2	85	15
0.03	0.1	80	20
0.03	0.02	66	34
0.03	0.002	58	42

[a] Yields are 60–75% obtained by NMR integration using benzene as an internal standard. [b] The methyl hypochlorite in methylene chloride was added dropwise to the olefin under nitrogen and ultraviolet illumination.

14 and 15. Further support for a radical intermediate is obtained from the following dilution experiment. As the concentration of the olefin is decreased, the amount of 1,5 product is increased (Table II). These results show that there is an equilibrium of the cyclopropylcarbinyl and homoallyl intermediates which is consistent only with a radical process.

The chlorination of 4 with iodobenzene dichloride (IBD) gave primarily products 7 and 12 from a molecule induced homolysis reaction. A radical process was confirmed by a dilution experiment (Table I, runs 11–16). We were unable to inhibit the radical pathway completely using oxygen as the inhibitor as indicated by the large amount of 1,5 product 12 when 4 was treated with IBD under ionic conditions (Table I, run 10).[14]

When 4 is treated with trichloroamine, products 7, 8, and 9 are apparently formed by an ionic rather than a radical mechanism (Table I, runs 17–20). Formation of 8 and 9 is not consistent with a radical process since it would involve loss of a hydrogen atom from a radical intermediate. Apparently

products 8 and 9 are formed by loss of a proton from a cyclopropylcarbinyl cation intermediate to generate hydrogen chloride. Additional support for an ionic process comes from the absence of the 1,5 product (12), the insignificant change in product distribution as the concentration of the reagents is decreased (runs 19 and 20), and from the similar product distributions for the addition of chlorine and NCl_3 to 4. In the case of NCl_3, product 10 is probably not formed because the hydrogen chloride, which is generated during the reaction, reacts with NCl_3 to form ammonium chloride.[15] We assume that the reaction of NCl_3 with 4 proceeds by an ionic mechanism because a very stable cyclopropylcarbinyl cation intermediate can be formed. This agrees with Kovacic's observation[9a] of a large ionic component for the reaction of NCl_3 with olefins such as isobutylene and norbornene which are also able to form stable cation intermediates.

Experimental Section

General. Vinylcyclopropane (1) was prepared by the pyrolysis of 1-cyclopropylethyl *S*-methyl xanthate as reported by Overberger.[16] 2-Cyclopropylpropene (4) was prepared by dehydration of dimethylcyclopropylcarbinol over sulfuric acid.[17] All other reagents and solvents were obtained commercially. Neat bromine was added from a small capillary dropper to magnetically stirred solutions. Chlorine was condensed in a calibrated capillary tube, and then allowed to distill into a stream of carrier gas (N_2 or O_2) which was bubbled into the reaction mixture. The initial reaction mixture contained an excess (10–40%) of 1 or 4. Control experiments show that the 1,2 products are stable under the reaction conditions. Removal of the solvent and excess olefin was carried out on a rotary evaporator at room temperature and the product composition was determined by NMR analysis. The yields were determined by adding 30 μl of a 1.0 M solution of benzene, toluene, or 1,2-dichloroethane in CCl_4 as an internal standard to the crude products dissolved in ca. 300 μl of CCl_4. Nuclear magnetic resonance spectra were obtained on a Varian T-60A spectrometer and the infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer. The VPC analysis was accomplished on a Hewlett-Packard 5750 flame ionization chromatograph. Collection of products by VPC was accomplished on an F and M 700 chromatograph. The following columns were used: column A, 6 ft × 0.25 in. stainless steel column of 5% SE-30 on 60/80 Chromosorb W; Column B, 12 ft × 0.25 in. 10% Carbowax 20M on Chromosorb W.

Reaction of Bromine with 1. To 38 mg (0.56 mmol) of 1 in a weighed amount of solvent (Table I) at −15 °C was added ca. 25 μl of neat bromine. The solvent was removed at room temperature on a rotary evaporator and an NMR spectra recorded to obtain the yield (100%) and product ratios (Table I). These NMR solutions were found to be stable at room temperature for several days. Several analytical runs were combined and short-path distillation gave **2a**, bp 45–47 °C (0.75 mm), with the following spectral properties: ir (CCl_4) 3090 (c-C_3H_5), 2940 (C–H), 1440 (C–H), 1130, 1015 (c-C_3H_5), 925 cm^{-1}; NMR (CCl_4) δ 0.30–1.0 (m, 4 H), 1.07 (m, 1 H), 3.6–4.0 (m, 3 H). The 1,5 product (3a) was not obtained free of **2a** by distillation. When **2a** was analyzed by VPC a mixture, ca. 50:50, of **2a** and **3a** was obtained.[10] The retention times for **2a** and **3a** were 14 and 25 min, respectively, on column A at 75 °C.

Isomerization of 2a to 3a. To a 70-mg (0.31 mmol) mixture of **2a** and **3a** (8:1, respectively) in 0.3 ml of reagent acetone at room temperature was added 15 mg of $ZnBr_2$.[12] After 2 h the reaction mixture was poured into 1.0 ml of water, extracted with three portions of methylene chloride, and dried over $MgSO_4$. The solvent was removed at reduced pressure, and a bulb-to-bulb distillation of the clear oil at 0.5 mm with an oil bath maintained at 60 °C gave 50 mg (72%) of a clear oil with the same VPC retention time as reported above for **3a** on column A. The following spectra were obtained: ir (CCl_4) 3030, 2970, 1670, and 1430 (C–H), 1255, 1200, 965 (C–H), 930 cm^{-1}; NMR (CCl_4) δ 2.63 (m, 2 H), 3.38 (t, J = 6.8 Hz, 2 H), 3.86 (m, 2 H), 5.78 (m, 2 H).

Reaction of Bromine with 4. The bromination was carried out on ca. 60-mg samples as described above. The yield (90%) and the product ratios were determined by NMR. A preparative reaction was carried out by adding 8.6 g (0.054 mol) of bromine dropwise to 4.92 g (0.06 mol) of 4 in 125 ml of pentane. The reaction mixture was maintained at −15 °C in an isopropyl alcohol bath by adding dry ice to the alcohol bath as needed. The solvent was removed on a rotary evaporator, and distillation[18] gave 5 (bp 41.0–41.5 °C, 0.5 mm) with the following spectral properties: ir (neat) 3090 (c-C_3H_5), 3000 (C–H), 1440 and 1370 (C–H), 1230, 1120, 1065, 1020 (c-C_3H_5), 895, 620, 590, and 565 cm^{-1} (C–Br); NMR (CCl_4) δ 0.30–0.85 (m, 4 H), 1.20 (m, 1 H), 1.75 (s, 3 H), 3.94 (s, 2 H).

Isomerization of 5. To 3.63 g (0.015 mol) of 5 in 15 ml of acetone was added 50 mg of $ZnBr_2$.[12] The reaction mixture was stirred at room temperature for 30 min at which time it was poured into 50 ml of water. The products were isolated as described above for **3a**. An NMR spectra of the crude oil showed that the products 6-(*Z*) and 6-(*E*) were formed in a 3:7 ratio, respectively.[19] Distillation gave 3.00 g (82%) of a mixture of 6-(*Z*) and 6-(*E*) (bp 64–67 °C, 0.65 mm) with the following properties: ir (neat) 3010 (C–H), 2960 (C–H), 1660 (C=C), 1445 (C–H), 1270, 1205, 750 (C–H), 610 cm^{-1}; NMR (CCl_4) δ 1.80 and 1.87 (two quartets, J = 0.6 and 1.1 Hz, respectively, 3 H), 2.62 (q, J = 6.6 Hz, 2 H), 3.34 (t, J = 6.6 Hz, 2 H), 3.90 (br s, 2 H), 5.55 (m, 1 H).

Chlorination of Vinylcyclopropane 1. The reactions were carried out at −15 °C in the dark in a solution which was 0.02 mole fraction in 1 (60–70 mg). Chlorine (20 μl) was distilled into a stream of oxygen and was bubbled into the reaction mixture. Analysis by VPC on column A at 55 °C gave products **2b** and **3b** with retention times of 8.0 and 16 min, respectively.[20] Analysis of the crude mixture by NMR showed that the products were formed in 40% yield and that the product ratios were similar to those obtained by VPC (Table I). The products were obtained pure by VPC collection on column A, and the following spectral properties were recorded: **2b**, ir (CCl_4) 3090 (c-C_3H_5), 2960 (C–H), 1440 (C–H), 1180, 1050, 1020 (c-C_3H_5), 950, 920, 900 cm^{-1}; NMR (CCl_4) δ 0.30–0.90 (m, 4 H), 0.95–1.3 (m, 1 H), 3.2–3.9 (m, 3 H); **3b**, ir (CCl_4) 3010 (C–H), 2960 (C–H), 1630 (C=C), 1440 (C–H), 1250, 970 cm^{-1} (C–H); NMR (CCl_4) δ 2.57 (m, 2 H), 3.52 (t, J = 6.8 Hz, 2 H), 4.00 (m, 2 H), 5.77 (m, 2 H).

Isomerization of 2b. To a 25-mg (0.18 mmol) mixture of **2b** and **3b** (8:1, respectively) in 0.3 ml of reagent acetone was added 15 mg of $ZnCl_2$.[12] After 1.5 h the products were isolated as described above for the isomerization of **2a**. Bulb-to-bulb distillation of the product at 10.0 mm with an oil bath maintained at 60 °C gave 20 mg of a clear oil with the same VPC retention time and spectra as reported above for **3b**.

Reaction of Chlorine with 4. A. Ionic Conditions. The chlorination was carried out on ca. 60 mg (0.02 mole fraction) of 4 as described above for the chlorination of 1. The yields (32%) and product ratios were determined by NMR. Several of the analytical runs were combined and the products collected by preparative VPC. Product **7** was collect on column A and had a retention time of 9.0 min at 42 °C. The 1,2-dichloride **7** had the following spectral properties: ir (neat) 3090 (c-C_3H_5), 2980 (C–H), 1450 (C–H), 1430, 1370 (C–H), 1135, 1080, 1020 (c-C_3H_5), 905, 825, 785, 705 cm^{-1}; NMR (CCl_4) δ 0.35–0.70 (m, 4 H), 1.22 (m, 1 H), 1.59 (s, 3 H), 3.74 (s, 2 H). Products **8**, **9**, and **10** had retention times of 11, 15, and 9 min, respectively, on column B at 62 °C and gave the following spectral properties: **8**, ir (CCl_4) 3085 (c-C_3H_5), 3010 (C–H), 2930 (C–H), 1640 (C=C), 1440 and 1370 (C–H), 1205, 1075, 1020 (c-C_3H_5), 925, 905, 815 cm^{-1}; NMR (CCl_4) δ 0.35–0.70 (m, 4 H), 1.30 (m, 1 H), 1.63 (d, J = 1.3 Hz, 3 H), 5.78 (p, J = 1.3 Hz, 1 H); **9**, ir (CCl_4) 3085 (c-C_3H_5) 3010 (C–H), 2970 (C–H), 1640 (C=C), 1445 (C–H), 1425 (C–H), 1260, 1020 (c-C_3H_5), 905 (C–H), 710 cm^{-1}; NMR (CCl_4) δ 0.40–0.83 (m, 4 H), 1.22 (m, 1 H), 4.02 (d, J = 0.9 Hz, 2 H), 4.79 (m, 1 H), 5.00 (dd, J = 1.7 and 0.9 Hz, 1 H); **10**, ir (neat) 3085 (c-C_3H_5), 2960 (C–H), 1450 and 1360 (C–H), 1290, 1260, 1230, 1150, 1113, 1020 (c-C_3H_5), 995, 885, 780, 655, and 595 cm^{-1}, in reasonable agreement with the Raman spectrum[21] reported for **10**; NMR (CCl_4) δ 0.40–0.60 (m, 4 H), 1.10 (m, 1 H), 1.52 (s, 6 H).

B. Radical Conditions. Reactions were carried out at −15 °C on a solution which was 0.50 mole fraction in 4 (250 mg of 4 in 300 mg of CCl_4). Oxygen was removed by bubbling nitrogen gas through the reaction mixture for ca. 3 min. The reaction flask was illuminated with a 275-W General Electric lamp. Chlorine (20 μl) was distilled into the stream of nitrogen carrier gas. The crude reaction mixture was analyzed by NMR as described above (30% yield), and found to contain products **7**, **8**, **9**, and **10** in a ratio of 2.1:1.0:1.8:1.4, respectively.

Isomerization of 7. To 700 mg of dichloride 7 in 0.5 ml of reagent acetone was added 50 mg of fused $ZnCl_2$.[12] After 30 min at room temperature the reaction mixture was poured into 15 ml of water and the products were isolated as described above for the isomerization of **2a**. An NMR spectra of the crude oil showed that the products 12-(*Z*) and 12-(*E*) were formed in a ratio of 1:5, respectively.[19] Distillation gave 0.560 g (80%) of the mixture (bp 73–76 °C, at 8.0 mm) with the following spectral properties: ir (neat) 3010 (C–H), 2960 (C–H), 1660 (C=C), 1440 and 1380 (C–H), 1290, 1260, 1160, 1080, 940, 910, 830, 810, 790, 720, 680 cm^{-1}; NMR (CCl_4) δ 1.78 and 2.00 (two quartets, J = 0.8 and 1.0 Hz, respectively, 3 H), 2.53 (q, J = 6.8 Hz, 2 H), 3.46 (t, J = 6.8 Hz, 2 H), 3.97 (br s, 2 H), 5.55 (m, 1 H).

Reaction of Hydrochloric Acid with 4. To 820 mg of 4 in 30 ml

of methylene chloride at −15 °C was bubbled HCl gas for 1 min. The reaction mixture was allowed to warm to room temperature and the solvent was then removed on a rotary evaporator. Analysis of the crude mixture by NMR showed only **10** and unreacted **4**. Distillation gave 660 mg of pure **10** [bp 45–47 °C, 60 mm (lit.[22] 104–105 °C, 760 mm)] with the properties reported above.

Isomerization of 10. To 600 mg of **10** in 2.0 ml of anhydrous ether was added 50 mg of fused $ZnCl_2$.[12] The reaction mixture was stirred for 5 h at 25 °C. Workup as described for the isomerization of **2a** above gave pure **11** [bp 82–83 °C, 100 mm (lit.[22] 131–133 °C, 760 mm)] with the same spectral properties reported for 5-chloro-2-methyl-2-pentene.[22]

Reaction of Methyl Hypochlorite with 4. A. Ionic Conditions. Oxygen was bubbled through a solution of 585 mg (7.15 mmol) of **4** in 13.5 ml of anhydrous methanol at 0 °C for 2 min. To this stirred solution, under an oxygen atmosphere, in the dark, was added dropwise 4.0 ml of a 1.4 M methyl hypochlorite solution in methylene chloride. The reaction mixture was poured into 100 ml of ice water, extracted with methylene chloride, and dried over $MgSO_4$. The yield by NMR analysis of the crude mixture using benzene as an internal standard showed the products to be formed in 75% yield. The product ratios were 1.0:1.2:5.0 for **8**, **9**, and **13**, respectively. Distillation gave pure **13** (bp 70–72 °C, 24 mm) with the following spectral properties: ir (neat) 3080 (c-C_3H_5), 2950 (C–H), 1460 and 1375 (C–H), 1100 (C–O), 1013 (c-C_3H_5), and 750 cm^{-1}; NMR (CCl_4) δ 0.20–0.60 (m, 4 H), 0.7–1.1 (m, 1 H), 1.05 (s, 3 H), 3.24 (s, 3 H), 3.44 (s, 2 H). A similar reaction was carried out at 25 °C for 3 h in methylene chloride as the solvent. The solvent was removed on a rotary evaporator at room temperature. Analysis by NMR showed the product ratio for **7**,[23] **8**, **9**, and **13** to be 1:5:4:5, respectively. Product **13** (100 mg) was found to be stable when treated with 30 mg of fused $ZnCl_2$ in 0.3 ml of anhydrous ether at 25 °C for 48 h.

B. Radical Conditions. Reactions of methyl hypochlorite under radical conditions were carried out at the mole fractions of **4** in methylene chloride listed in Table II. To 655 mg (8.0 mmol) of neat **4** at 0 °C, under nitrogen and ultraviolet illumination, was added 4.0 ml of a 0.08 mole fraction (1.4 M) methyl hypochlorite solution in methylene chloride. The solvent was removed at reduced pressure and NMR analysis showed only product **14**. Product **15** was also formed when the reaction was carried out under dilute conditions (Table II). Distillation gave pure **14** (76%) (bp 56–60 °C, 20 mm): ir (neat) 3080 (c-C_3H_5), 2950 (C–H), 1450 and 1380 (C–H), 1270, 1105 (C–O), 1015 (c-C_3H_5), 815, and 760 cm^{-1}; NMR (CCl_4) δ 0.30–0.70 (m, 4 H), 0.9–1.2 (m, 1 H), 1.46 (s, 3 H), 3.36 (s, 3 H), 3.42 (s, 2 H).

Isomerization of 14. To 0.500 g of **14** in 1.0 ml of anhydrous ether was added 60 mg of fused $ZnCl_2$.[12] The reaction mixture was stirred for 5 min at 25 °C and then isolated as described above for the isomerization of **2a**. Analysis by NMR on the crude mixture showed **15**-(*Z*) and **15**-(*E*) to be formed in a ratio of 1:4, respectively.[19] Distillation gave 0.405 g of the mixture **15**-(*Z*) and **15**-(*E*) (81%) (bp 115–121 °C, 25 mm): ir (neat) 3000 (C–H), 2940 (C–H), 1440 and 1430 (C–H), 1295, 1190, 1110, 1095, 790, 765, 715, and 660 cm^{-1}; NMR (CCl_4) δ 1.63 and 1.76 (br singlets, 3 H), 2.53 (q, J = 7.0 Hz, 2 H), 3.20 (s, 3 H), 3.47 (t, J = 7.0 Hz, 3 H), 3.72 (br s, 2 H), 5.35 (m, 1 H).

Reaction of Iodobenzene Dichloride with 4. A. Ionic Conditions. The reaction mixture [0.006 mole fraction **4** (3.0 mmol) in methylene chloride as solvent] was prepared at 0 °C, in the dark, under O_2, as described for the ionic reaction of methyl hypochlorite above. IBD (0.9 mmol) was added as a solid. The reaction mixture was allowed to come to room temperature and then stirred under an oxygen atmosphere for 20 h. Removal of the solvent on a rotary evaporator at room temperature followed by NMR analysis showed the products (70%) **7**,[23] **8**, **9**, **10**, and **12** to be formed in a ratio of 6.3:1.3:1.0:1.1:4.6, respectively.

B. Radical Conditions. The reactions were carried out under the radical conditions described for the reaction of methyl hypochlorite to **4** above. To IBD (3.0 mmol) in methylene chloride at 25 °C (mole fractions given in Table I) was added 0.5 ml of a 6.0 M solution of **4** in methylene chloride. The reaction mixture was stirred for ca. 3 min and the solvent was removed as described above. Analysis by NMR gave yields of ca. 75%. The product ratios[23] for each dilution are given in Table I.

Reaction of Trichloroamine with 4. To 265 mg (3.2 mmol) of **4** in methylene chloride or carbon tetrachloride (mole fraction **4** given in Table I) at −15 °C was added dropwise 2.7 ml of a 0.34 M solution of NCl_3 in methylene chloride or carbon tetrachloride. The reaction was carried out under the ionic and radical contions described above. The solvent was removed at room temperature on a rotary evaporator after all the NCl_3 was added. Analysis by NMR on the crude mixture showed yields of ca. 95%. The product ratios[23] are given in Table I.

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Registry No.—**1**, 693-86-7; **2a**, 58673-27-1; **2b**, 58673-28-2; **3a**, 58673-29-3; **3b**, 58673-30-6; **4**, 4663-22-3; **5**, 58673-31-7; (*Z*)-**6**, 58673-32-8; (*E*)-**6**; 58673-33-9; **7**, 58673-34-0; **8**, 5296-54-8; **9**, 4216-98-8; **10**, 58673-35-1; **11**, 7712-60-9; (*Z*)-**12**, 58673-36-2; (*E*)-**12**, 58673-37-3; **13**, 58673-38-4; **14**, 58673-39-5; (*Z*)-**15**, 58673-40-8; (*E*)-**15**, 58673-41-9; bromine, 7726-95-6; chlorine, 7782-50-5; methyl hypochlorite, 593-78-2; hydrochloric acid, 7647-01-0; iodobenzene dichloride, 932-72-9; trichloroamine, 10025-85-1.

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(10) Rearrangement of the 1,2 products to the 1,4 products was substantial in the VPC even when on column injection, or when a glass-lined injector oven was used.

(11) Slobodin[11] treated the reaction mixture **2a** and **3a** with base and obtained cyclopropylacetylene in 94% yield. Because of the high yield, Slobodin assumed that both **2a** and **3a** reacted to give cyclopropylacetylene. We repeated this reaction and found that cyclopropylacetylene was formed in high yield from **2a**, but no volatile products were found when **3a** was treated with base under the same conditions.

(12) Structural assignments of the products are based on their spectral properties and rearrangement of the 1,2 products to the 1,5 products with zinc salts. For rearrangement of cyclopropylcarbinyl alcohols and 1,2-dihalides with zinc salts, see M. Julia, Y. Noel, and R. Guegan, *Bull. Soc. Chim. Fr.*, 3742 (1968); M. Julia and Y. Noel, *ibid.*, 3749, 3756 (1968); A. N. Pudovik, *Zh. Obshch. Khim.* **19**, 1179 (1949); *Chem. Abstr.*, **44**, 1005 (1950).

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(18) Distillation was discontinued after about one-third of the product distilled because of extensive decomposition in the distilling flask.
(19) The configurations of the *E* and *Z* isomers were assigned on the basis of their NMR spectra. The chemical shift of a methyl group in a trisubstituted olefin generally resonate about 0.1 ppm downfield when the methyl group is in a cisoid configuration relative to the vinyl hydrogen. The allylic coupling of the methyl group with the vinyl hydrogen is generally larger in the cisoid configuration by approximately 0.3–0.6 Hz. See L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2d ed, Pergamon Press, Elmsford, N.Y., 1969, pp 225 and 316.
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Kinetics of the Hydrolysis of Fluoromethyl Methyl Ether in Neutral to Alkaline Solution[1a]

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The kinetics of the hydrolysis of fluoromethyl methyl ether have been determined in aqueous solution at 25 °C in the pH range 7–13 by following the rate of release of hydrogen ions. The reaction is simple first order with k = 1.6–2.1 × 10^{-3} s^{-1} and shows no mass law effect in the presence of 0.1 M NaF. The mechanisms of hydrolysis consistent with these facts are discussed and compared to those for chloromethyl methyl ether, bis(chloromethyl) ether, and glycosyl halides.

As a part of a study of the stepwise mechanisms of carbonyl group addition–elimination reactions, we initiated a study of the kinetics of the hydrolysis of fluoromethyl methyl ether (FME). In particular, we had hoped to establish the relative reactivities of various nucleophiles toward the methoxymethyl cation as a model for nucleophilicity toward a protonated carbonyl group. In the limited study reported here this goal has not been realized, and further work has been postponed at least temporarily because of the demonstrated carcinogenic nature of the related chloromethyl methyl ether, which is used as the starting material for the preparation of the title compound, and the possible toxicity of FME itself.[2] However, since there are no reports (known to us) of quantitative studies of the hydrolysis of simple α-fluoroalkyl ethers, these results are of interest for comparison with the hydrolysis of chloromethyl methyl ether,[3] and with the chemical[4] and enzymatic[5] hydrolyses of glycosyl fluorides.

Experimental Section

Preparation and Characterization of Fluoromethyl Methyl Ether. The method of preparation is that of Via,[6] and is similar except for solvent to that described by Tullock and Coffman.[7] A total of 70 g (0.9 mol) of chloromethyl methyl ether (Eastman) was added over a period of 12 h to a refluxing suspension of 82 g (2 mol) of sodium fluoride (Baker analytical reagent, powder form) in 500 ml of purified[8] acetonitrile. A small distillation head was mounted atop the reflux condenser, and the low-boiling FME collected with a dry ice cooled Dewar condenser, with the collection flask also cooled by dry ice. About 25 ml of a water-white product was collected in this way, then transferred to and sealed in Pyrex ampules, and stored at −20 or −70 °C. The above operations were carried out with a nitrogen atmosphere.

The product thus obtained is very temperature sensitive. If the ether was allowed to stand (in a sealed vessel) at 0 °C for a short time, the color of the product changed to yellow and then deep red. Even at −20 °C the material in the ampules took on a yellow color (unless a small amount of triisopropylamine had been added). Furthermore, attempts to use a "cow" type distilling receiver resulted in decomposition of the product and deposition in the receiver of a white solid (uncharacterized, but probably paraformaldehyde).

The FME used in the analyses and in the kinetics experiments described below was redistilled in a trap-to-trap manner at atmospheric pressure under nitrogen, with the receiver cooled with liquid nitrogen and the pot in ice. In some cases a small amount of triisopropylamine was added to the pot since this seemed to aid the distillation. The redistilled ether was stored at −70 °C. For the kinetic studies described below, a solution of FME in anhydrous methanol was prepared by adding 5 ml of dry ice chilled methanol to about 1.5 ml of redistilled FME and was stored at −78 °C in a 14/20 ⅋-stoppered heavy-walled test tube.

The purity of the redistilled FME was checked by GLC and ^{1}H NMR analyses. With an Aerograph Hy-Fy gas chromatograph, which has a hydrogen-flame detector, we found that we could obtain excellent resolution of reactants and products using a 5 ft × 0.125 in. column of 15% XF-1150 on 60–80 Chromosorb W at room temperature. Samples were introduced by using a dry ice cooled 10-μl Hamilton syringe to quickly take an aliquot of ether from a dry ice–acetone cooled flask and inject it into the chromatograph. The redistilled FME yielded four well-resolved peaks that in order of increasing retention time had relative areas of 15:3:1:~0.1. The first peak is assumed to be due to FME. The second and third peaks have retention times identical with those of dimethoxymethane and acetone, respectively. The fourth peak was not assigned, but it was demonstrated that this peak was not due to chloromethyl methyl ether, acetonitrile, or methanol. GLC analysis of the chloromethyl methyl ether starting material showed that it contained a small amount of a contaminant with the same retention time as dimethoxymethane. The acetone in the product probably arose from the opening of the flask containing the fluoro ether while it was suspended in a dry ice–acetone bath, since it did not come from the cooling of the syringe.

The ^{1}H NMR spectrum of a mixture of the redistilled FME plus Me_4Si in a tightly stoppered heavy-walled NMR tube was obtained at about −50 °C using a Varian A-60 NMR spectrometer. The spectrum is consistent with the structure of FME, and indicates very small amounts of dimethoxymethane and acetone contaminants. Observed peaks were assigned as follows: A singlet at δ 2.17 was increased in size by the addition of acetone and is therefore assigned to hydrogens of

acetone. Singlets at δ 3.43 and 4.73, relative areas 3.08, were assigned to the methyl and methylene hydrogens of dimethoxymethane by comparison with the peak positions in the spectrum of an authentic sample of this compound. A singlet at δ 3.65 and a doublet (J = 60 Hz) centered at δ 5.45, relative areas 1.48, were assigned to the methyl and methylene hydrogens of FME. The observed coupling constant is consistent with a geminal ^{19}F–^{1}H coupling, e.g., in β-fluoroethanol for geminal ^{19}F–^{1}H coupling J = 46.7 Hz.[9] On the basis of these assignments, the composition of the redistilled ether is 201:13.5:1 FME:dimethoxymethane:acetone. The FME is thus about 95% pure, and contains no detected impurity that would be expected to interfere with the kinetic studies.

Other Reagents. Sodium perchlorate was Smith "anhydrous", which was ground into small lumps and dried at 130 °C for 4 h[10] before weighings. Although 0.5 M solutions of sodium fluoride and 1.0 M solutions of sodium perchlorate were slightly basic; titration with standard HCl indicated an insignificant (for our purposes) basic contaminant. A 0.481 M formaldehyde solution was prepared by dissolving (by heating to 80 °C under nitrogen) 73 g (0.083 mol) of trioxane in 100 ml of 0.001 M $HClO_4$, and diluting this solution to 500 ml. Basified aliquots of the formaldehyde were treated with iodine, and the iodine consumed in formaldehyde oxidation determined by comparison of the thiosulfate titre with that for an iodine blank.[11] Baker analytical reagent grade iodine ("100.0% I_2") was used as a primary standard to standardize sodium thiosulfate solution prepared from Fisher Certified A.C.S. grade $Na_2S_2O_3 \cdot 5H_2O$.

Procedure for Kinetic Runs. A "25-ml" three-neck flask with 14/20 ⅁ joints was used as the reaction flask. The center neck held one of the special stoppers described below, and the outer necks held glass and reference electrodes, which were positioned so that their tips were about 0.75 in. from the bottom of the flask. Even with the electrodes and a 1-in. Teflon-coated stirring bar in place, the capacity of the flask was about 35 ml. The flask was immersed to the necks in a shallow constant-temperature bath maintained at 25 ± 0.2 °C that sat atop a magnetic stirrer and was also stirred with a 1-in. magnet. With this apparatus very rapid stirring speeds were possible.

The pH of the reaction solution was monitored using a Beckman Research Model pH meter, and Beckman No. 39004 Type E-2 glass and No. 39071 fiber-junction calomel reference electrodes. Using these same electrodes but a Beckman Zeromatic pH meter, a change in pH from 13.00 to 11.7 caused by rapid addition of a small aliquot of ~10 M HCl to a rapidly stirred solution of 0.1 M NaOH is limited by the response time of the meter (~5 s). At pH's >7 we observed no interference by fluoride ion. During a kinetic run the pH of the unbuffered reaction solution was continuously monitored by using a Leeds-Northrup Speedomax H Model S strip-chart recorder with a chart speed of 0.5 in./min. The chart could be read with a precision of about 0.002 pH units, and readings obtained from the recorder agreed with those obtained directly from the meter with a maximum deviation of 0.05 pH units.

In order to allow convenient transfer by syringe of aliquots of the methanolic FME solution, we constructed gas-cooled septum stoppers. A 14/35 ⅁ inner joint, 10 cm long, was cut to the dimensions of a 14/20 joint using a glass saw, so that the bottom of the joint was left flat. A 0.125 in. thick Teflon disk with a 1.5-mm center hole was fastened with epoxy cement inside the joint and flush with the end, and then a silicone-rubber GLC septum fastened to the bottom of the joint with "Silastic Clear Sealer" (a Dow-Corning product). A small side arm through which cold nitrogen could be admitted was added about 0.5 in. above the top of the joint. One of these stoppers was used in the reaction flask, and another in the stock solution flask. Nitrogen gas cooled in a 0.25 in. i.d. × 10 ft copper coil immersed in liquid nitrogen was passed through the stoppers in order to cool a 1.0-ml or a 50-μl syringe during transfers of the stock solution. The temperature within the stopper could be brought as low as −100 °C.

To make a run, the pH meter and electrodes were first checked with a series of standard buffers. Then the reaction flask was charged with 30.0 ml of a solution of sodium hydroxide and sodium fluoride or perchlorate, and the solution stirred to allow it to come to temperature equilibrium. Cold nitrogen gas was started flowing through the stoppers in the reaction flask and fluoro ether stock solution flask. The pH recorder was started and standardized at pH = log $[OH^-]^0$ − 14.00, and after a steady baseline was reached, an aliquot of the methanolic fluoro ether was added and the nitrogen turned off. The pH was monitored until it no longer continued to change.

For the hydrolyses in 0.1 M sodium hydroxide, 0.80–85 ml of the methanolic FME solution was added to 30.0 ml of a solution 0.10 M in sodium hydroxide and 0.10 M in either sodium fluoride or sodium perchlorate. Addition of the ether solution to the sodium hydroxide caused an immediate drop in pH of 0.04–0.06 units, which is equivalent to 9–13% of the total acid released and which is probably a result of partial solvolysis of the FME in the stock solution. Useful data were obtained after allowing 1 min for the pH vs. time slope to stabilize. For the run in 10^{-3} M sodium hydroxide, the addition of 17 μl of the FME solution to the hydrolysis solution caused an immediate pH drop of ~0.4 units, which amounts to about 50% of the total acid released. Useful data were obtained after allowing 1 min for the pH vs. time slope to stabilize.

Results

Since the overall stoichiometry of the hydrolysis of FME is

$$CH_3OCH_2F + H_2O \rightarrow CH_2(OH)_2 + CH_3OH + H^+ + F^-$$

the rate of the hydrolysis can be obtained from the change in pH of the reaction solution with time. Under the basic conditions used up to 30% of the formaldehyde will be present as the hemiacetal with methanol, and therefore at basic pH's acid dissociation of formaldehyde hydrate and hemiacetal must be allowed for, and at lower pH's the protonation of fluoride ion taken into account. Depending on the pH of the hydrolysis medium two slightly different methods were used, both of which are based on the preparation of standard curves of pH vs. extent of reaction.

For hydrolyses in solutions that were initially 0.1 M in sodium hydroxide, values of the apparent pH, i.e. pH uncorrected for sodium ion response, were converted into degree of reaction by using a standard curve that was obtained by measuring the apparent pH's of a series of "synthetic reaction solutions". That is, we prepared solutions of sodium hydroxide, sodium fluoride, formaldehyde, and methanol such that

$$[OH^-]_{stoich} = 0.1 - \alpha$$

$$[F^-] = 0.1 + \alpha$$

$$[CH_2(OH)_2]_{stoich} = \alpha$$

$$[CH_3OH]_{stoich} = 0.5 + \alpha$$

where the subscript "stoich" indicates that the concentrations are stoichiometric or concentrations by mixing, and α is a parameter that represents the amount of FME hydrolysis, and equals $[CH_3OCH_2F]^0 - [CH_3OCH_2F]^t$. The apparent pH of each of these synthetic reaction solutions was measured, and plotted vs. log $[OH^-]_{stoich}$. The curvature of the plot at the higher pH's is that expected as a result of sodium ion response of the glass electrode and dissociation of formaldehyde hydrate and methoxymethylcarbinol. Using an expanded-scale version of this plot for the hydrolysis of FME in 0.1 M sodium hydroxide, the apparent pH at a given time was converted into a value of $[OH^-]_{stoich}$, and the plots of ln ($[OH^-]_{stoich} - [OH^-]^{\infty}_{stoich}$) vs. time prepared. Such plots for three experiments are shown in Figures 1 and 2. The first-order rate constants for FME hydrolysis obtained from the slopes of these plots are shown in Table I.

A similar method was used for the single run where the initial $[OH^-] = 10^{-3}$ M. A 30-ml aliquot of the sodium hydroxide–sodium fluoride solution was titrated potentiometrically with 0.0160 M hydrochloric acid using a buret graduated to 0.02 ml, and an expanded scale titration curve plotted. The experimental apparent pH values at various times obtained in the kinetic experiment were converted into ml_t values, and ln ($ml_\infty - ml_t$) plotted vs. time.

Measurements of the rate of FME hydrolysis in more acidic solutions does not seem possible using the above method with the glass electrode since in these solutions the electrode response becomes erratic, probably because of the presence of HF_2^- ion, which attacks the electrode.

We have so far discussed only the overall stoichiometry of FME hydrolysis. Actually this hydrolysis is a multistep process that can be written

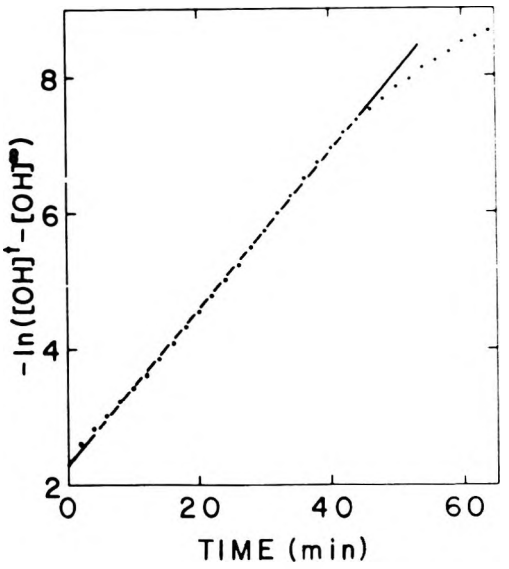

Figure 1. Plot of ln ($[OH^-]^t_{stoich} - [OH^-]^\infty_{stoich}$) vs. time for kinetic run where $[OH^-]^0_{stoich} = 0.1$ M and $[F^-]^0 = 0.1$ M.

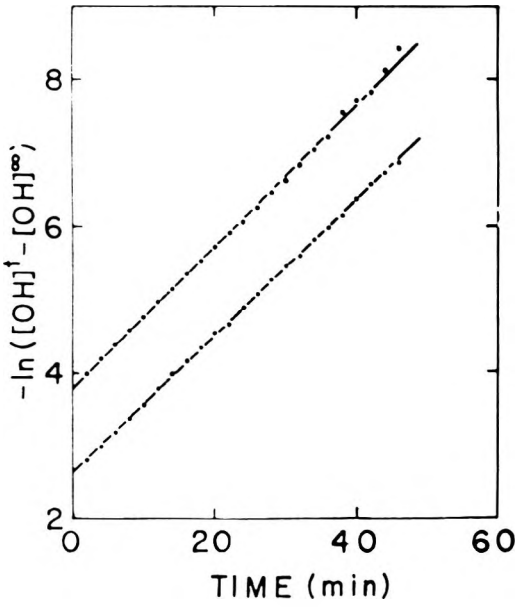

Figure 2. Plot of ln ($[OH^-]^t_{stoich} - [OH^-]^\infty_{stoich}$) vs. time for two kinetic runs where $[OH^-]^0_{stoich} = 0.1$ M, $[F^-]^0 = 0$, and $[ClO_4^-] = 0.1$ M. The upper line has been displaced upward by one ln unit.

$$CH_3OCH_2F + H_2O \underset{\beta_1}{\overset{k_1}{\rightleftharpoons}} CH_3OCH_2OH + H^+ + F^- \quad (1)$$

$$CH_3OCH_2OH \underset{\beta_2}{\overset{k_2}{\rightleftharpoons}} CH_2O + CH_3OH \quad (2)$$

$$CH_2O(+H_2O) \underset{\beta_3}{\overset{k_3}{\rightleftharpoons}} CH_2(OH)_2 \quad (3)$$

The use of standard curves to convert apparent pH to extent reaction involves the implicit assumption that reactions 2 and 3 are at equilibrium. We have examined this assumption in detail using computer modeling. The rate constants for reactions 2 and 3 are available in the literature. From Bell and Evans,[13] at 25 °C $\beta_3 = 1.6 \times 10^3[OH^-] + 5.1 \times 10^{-3}$, and thus since $K_{hyd} = 2 \times 10^3 = [CH_2(OH)_2]/[CH_2O]$,[14] $k_3 = 3.2 \times 10^6[OH^-] + 10$ (s^{-1}). From Le Hénaff,[15] at 20 °C $k_2 = 1.51 \times 10^3[OH^-] + 1.42 \times 10^{-3}$ and $K_{hemi} = 32 = ([CH_3OCH_2OH] \cdot [H_2O])/([CH_2(OH)_2][CH_3OH])$; thus $\beta_2 = (1.74 \times 10^6[OH^-] + 1.64)[CH_3OH]$ (s^{-1}). We will use these same values for 25 °C, and will treat $[CH_3OH]$ as a constant = 0.5 M, which is the concentration obtained by mixing 0.8 ml of methanol and 30 ml of reaction solution. Using the methods of Rodiguin and Rodiguina[16] we obtained expressions for the concentrations of CH_3OCH_2F, CH_3OCH_2OH, CH_2O, and $CH_2(OH)_2$ as a function of time, k_1 to k_3, and β_1 to β_3. Using $k_1 = 1.67 \times 10^{-3}$ s^{-1} and $\beta_1 = 0$, $[CH_3OCH_2F]^0 = 0.1$ M, and $[OH^-] = 0.1 - ([CH_3OCH_2F]^0 - [CH_3OCH_2F]^t)$ we found that even when $[CH_3OCH_2F]^t$ dropped to 10^{-7} M the ratios $[CH_2(OH)_2]/[CH_2O]$ and $[CH_2(OH)_2]/[CH_3OCH_2OH]$ were equal to the equilibrium ratios. Thus, for the hydrolysis of FME under the conditions described here step 1 is definitely rate limiting. It is interesting to note that a similar modeling of the hydrolysis of chloromethyl methyl ether using $k_1 = 1.0 \times 10^3$ (s^{-1}) and $[OH^-]$ = constant = 0.1 M shows that for this compound steps 2 and 3 would not be at equilibrium.

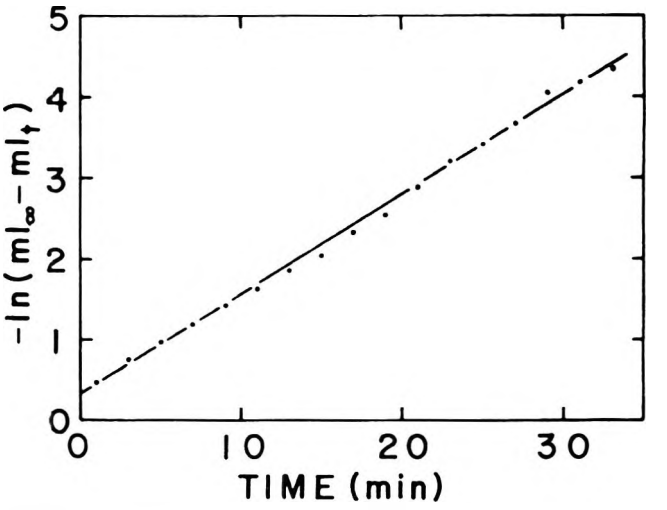

Figure 3. Plot of ln ($ml_\infty - ml_t$) vs. time for kinetic run where $[OH^-]^0_{stoich} = 10^{-3}$ M and $[F^-]^0 = 0.199$ M.

Table I. First-Order Rate Constants (s^{-1}) for Hydrolysis of Fluoromethyl Methyl Ether at 25 °C

$[F^-]^0$, M	$[OH^-]^0_{stoich}$, M	$[OH^-]^\infty_{stoich}$, M	k, s^{-1}
0.100	0.100	7.08×10^{-3}	1.92×10^{-3}
0[a]	0.100	1.57×10^{-2}	1.56×10^{-3}
0[a]	0.100	1.70×10^{-2}	1.61×10^{-3}
0.199	0.001	1.8×10^{-7}	2.06×10^{-3}

[a] $[NaClO_4] = 0.100$ M.

Discussion

We have found that in 0.1—2×10^{-7} M sodium hydroxide, the hydrolysis of FME is kinetically first order in fluoro ether only. These results can be accommodated by an SN1 mechanism of hydrolysis, eq 4

$$CH_3OCH_2F \xrightarrow{r.d.} CH_3OCH_2^+ + F^-$$
$$CH_3OCH_2^+ + (H_2O \text{ or } OH^-) \rightarrow (CH_3OCH_2OH \rightleftharpoons CH_2(OH)_2 + CH_3OH) + H^+ + F^- \quad (4)$$

where an intermediate resonance-stabilized methoxymethyl cation is formed and then captured by water or hydroxide ion, but not by fluoride ion. Such a mechanism would be analogous to that for the acid-catalyzed hydrolysis of formals and acetals.[17] Our results are also consistent with an SN2 mechanism, eq 5

$$CH_3OCH_2F + H_2O \xrightarrow{r.d.} (CH_3OCH_2OH \rightleftharpoons CH_2(OH)_2 + CH_3OH) + H^+ + F^- \quad (5)$$

in which water but not hydroxide ion directly displaces fluoride ion from the fluoro ether.

As noted in the introduction, if the mechanism were SN1 we had hoped to see a fluoride ion mass-law effect[18] that would allow relative nucleophilicities toward the methoxymethyl cation to be determined. This hope was based on the fact that the methoxymethyl cation is relatively stable and therefore might be selective in reacting with nucleophiles, and on the special stability of a geminal oxygen–fluorine grouping[19] that would result from fluoride ion return to re-form FME. However, attack on the cation by water or hydroxide ion has a similar driving force, and dominance by the latter nucleophiles may also be aided by the strong solvation expected for a small ion like fluoride. In acetone–water solvents, fluoride also fails to compete with water for triphenylcarbonium ion.[20] However, better nucleophiles like hydroxylamine and semicarbazide have been used to capture the dimethoxybenzyl cation $[PhC^+(OCH_3)_2]$ formed by acid-catalyzed hydrolysis of trimethyl orthobenzoate.[21] The lower rate of hydrolysis of FME in the presence of sodium perchlorate is probably a specific salt effect since it seems unlikely that perchlorate ion could compete with water for the capture of methoxymethyl cation.[22]

Both SN1 and SN2 mechanisms of α-halo ether solvolysis have been demonstrated. Jones and Thornton[3] have studied the solvolysis of chloromethyl methyl ether in a variety of solvents, including aqueous ethanol, acetone, and dioxane, and have concluded on the basis of the effect of solvent polarity (as measured by the Winstein–Grunwald m value) on rate, and substituent and solvent deuterium isotope effects, that a "SN1-like" mechanism of solvolysis operates. Ballinger et al.[23] had earlier arrived at a similar conclusion for solvolyses in ethanol and ethanol–ether mixtures on the basis that although added ethoxide ion caused a rate acceleration (much in excess of that caused by chloride or perchlorate ion) due to a parallel SN2 reaction, the magnitude of the acceleration was not so great as would be expected if the uncatalyzed solvolysis were SN2-like. Salomaa has compared the effect of structure on the hydrolysis of dialkoxymethanes and alkoxymethyl esters with that for the solvolyses in ethanol or ethanol–dioxane of alkoxymethyl chlorides and concluded that all three occur via alkoxymethyl cation intermediates.[24] Extrapolation of the results of Jones and Thornton[3] for solvolysis of chloromethyl methyl ether in aqueous dioxane to pure water yields $k = 6 \times 10^3\ s^{-1}$ at 25 °C, which is *at least* 3.5×10^6 times larger than the rate constant for unimolecular dissociation of FME. This leaving group effect can be compared to $k_{RCl}/k_{RF} = 1 \times 10^6$ for tritylhalide solvolysis in 85% acetone at 25 °C and $k_{RCl}/k_{RF} = 1 \times 10^5$ for *tert*-butyl halide solvolysis in 80% ethanol at 25 °C.[25]

Tou et al.[26] have studied the hydrolysis of bis(chloromethyl) ether, which because of the second chlorine hydrolyzes sufficiently slowly to be studied in pure water. The kinetics of the hydrolysis were studied in 1 and 2 M NaOH, 1 and 3 M HCl, and in pure water; in each case the hydrolysis was first order in ether only, and the rate constant for all conditions reasonably constant at about $2 \times 10^{-2}\ s^{-1}$. However, large changes in the parameters $\Delta S^{\ddagger}$ and $E^{\ddagger}$ accompanied the changes of reaction medium. Thus between 2 M NaOH and 3 M HCl, $\Delta S^{\ddagger}$ increased from −35.2 to −3.82 eu, and $E^{\ddagger}$ increased from 8.96 to 18.6 kcal/mol. Tou et al. interpreted these results to mean that the reaction mechanism changes from SN1 at high basicity to SN2 at high acidity. In the latter case they suggested that hydroxide ion displaces chloride ion from the protonated substrate. Such a mechanism seems unlikely since even if the acid dissociation constant of the protonated ether is 10^5 M, which assumes that bis(chloromethyl) ether is as basic as dimethoxymethane can be estimated to be,[27] the second-order rate constant for attack of hydroxide ion on the protonated ether must be $10^{17}\ M^{-1}\ s^{-1}$, which greatly exceeds the diffusion-controlled limit for recombination of hydroxide ions and protons, $1.4 \times 10^{11}\ M\ s^{-1}$.[28]

The results for simple α-haloalkyl ethers can be compared to those for glycosyl halides. The hydrolyses of a variety of glycopyranosyl fluorides have been found by Barnett[4] to be catalyzed by both H_3O^+ and OH^-, but no uncatalyzed reaction was reported. Hydrogen ion catalysis is attributed to assisted leaving of fluoride ion in an SN1 manner to yield a carbonium ion, which is captured by water to yield free sugar. In hydroxide ion solution, however, the reaction is SN2 like and results from attack of hydroxide ion or the C-6 hydroxyl (if there is one) at the carbon bearing fluorine. For four glycosyl fluorides that have the C-2 hydroxyls cis to the fluorine, at the minimum hydroxide ion concentration of 0.2 M and 20 °C, $k = 7.46\text{–}37.8 \times 10^{-5}\ s^{-1}$, and so for these glycosyl fluorides the uncatalyzed reaction is at least five times slower than with fluoromethyl methyl ether. (Use of the hydrogen ion catalyzed data does not lead to a different estimate.) For β-D-glucopyranosyl fluoride, in which the C-2 hydroxyl is trans to the fluorine, there is a rate acceleration relative to the α anomer of a few thousand fold, which is attributed to neighboring group participation by the hydroxyl. Various glycosyl fluorides are also hydrolyzed by enzymes whose normal function is hydrolysis[5] or phosphorolysis[29] of di- or polysaccharides. By contrast to glycosyl fluorides in methanol tetra-*O*-methyl-α-D-glucopyranosyl and mannopyranosyl chlorides solvolyze by an SN1 mechanism, and added methoxide ion leads to only a relatively small rate increase.[30]

Registry No.—FME, 460-22-0.

References and Notes

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Insertion of Fluoro Olefins into Carbon–Hydrogen Bonds to Yield 1:1 Adducts and Dehydrofluorination of the Adducts

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Tetrafluoroethylene and trifluoroethylene gave 1:1 adducts with isobutane under the influence of heat and in the absence of organic or inorganic initiators. Hexafluoropropene and chlorodifluoromethane gave $CF_2ClCF_2CHFCF_3$. Attempts to prepare 1:1 adducts between tetrafluoroethylene and chlorodifluoromethane resulted in cyclic dimerization of the tetrafluoroethylene. Dehydrofluorination of the adducts so obtained by means of solid potassium hydroxide afforded the corresponding fluoro olefins. NMR and mass spectral data are reported.

The investigation of radical additions to fluoro olefins other than tetrafluoroethylene and hexafluoropropene has been relatively little studied. Such investigations have mainly concerned reactions in which either a carbon–carbon bond or a carbon–hydrogen bond is formed together with a bond between carbon and a heteroatom.[1,2] Few reactions involving the simultaneous formation of both carbon–carbon and carbon–hydrogen bonds have been reported. These almost always involve the use of radical initiation catalysts such as *tert*-butyl peroxide, sodium peroxide, and azobisisobutyronitrile with the formation of predominantly telomeric products.[3-11] The reaction between fluoro olefins and alcohols has been investigated by Dedek and co-workers, who report the formation of 1:1 adducts between alcohols and chlorotrifluoroethylene under the influenee of γ irradiation (^{60}Co source).[12-15]

In the present work hexafluoropropene, tetrafluoroethylene, and trifluoroethylene have been found to insert into the carbon–hydrogen bonds of hydrocarbons such as chlorodifluoromethane and isobutane under the influence of heat alone (260–310 °C) to give good yields of 1:1 adducts (Scheme I). The conditions of thermal reactions are largely dependent

Scheme I

$$RH + CF_2CFX \xrightarrow{\Delta} RCF_2CHFX + HCF_2CFRX$$

I, $R = CF_2Cl$; $X = CF_3$ — Ia, $R = CF_2Cl$; $X = CF_3$

II, $R = Me_3C$; $X = F$ — IIIa, $R = Me_3C$; $X = H$

III, $R = Me_3C$; $X = H$

IV, $R = CF_2Cl$; $X = F$

upon the nature of the fluoro olefin employed. The operational temperatures and pressures are restricted because fluoro olefins can be dimerized individually to fluorinated cyclobutanes under the influence of heat. Hence tetrafluoroethylene reactions are generally confined to the temperature limits between 200 and 230 °C. Hexafluoropropene and trifluoroethylene reactions proceed favorably at temperatures in the range 260–320 °C.

Tetrafluoroethylene gave only a moderate conversion (20%) to 1,1,2,2-tetrafluoro-3,3-dimethylbutane (II) in the reaction with isobutane (ca. 1.5 atm) at 210 °C. Lower conversions (5–9%) to the structural isomers 1,1,2- and 1,2,2-trifluoro-3,3-dimethylbutane (III and IIIa) were obtained from a reaction between trifluoroethylene and isobutane even under higher reaction pressures (ca. 8 atm) and at temperatures in the range 210–280 °C. This lower reactivity of trifluoroethylene can be rationalized in terms of lower C–C π bond strengths of olefins containing vicinal fluorines.

The yields of III and IIIa were optimized (33%) by carrying out the reaction at elevated pressure (ca. 80 atm) at 280 °C. In this way minor quantities of some low-boiling liquid product and an appreciable quantity of high-boiling telomers were also obtained. The formation of telomers was partially inhibited when the mole ratio of hydrocarbon to fluoro olefin was increased from 3:1 to 6:1 (pressure ca. 134 atm), with a significant increase in the conversion to 1:1 adduct. Changing the mole ratios may not be the sole factor for the increased yield of the adducts, since the pressure is also much higher. Analysis by NMR and GLC showed the isomer ratios as 55:45 of III:IIIa.

The isomeric pair was separated from the reaction mixture by careful fractionation, and the two isomers were then separated by preparative GLC. The characteristic NMR spectra (^1H and ^{19}F) of compounds III, IIIa, and II are shown in Table I.

Chlorodifluoromethane reacted readily with hexafluoropropene at 275–280 °C under moderate pressures (ca. 8 atm) in the absence of any initiation catalyst, giving a relatively high yield of 1:1 adduct involving the carbon–hydrogen bond. The straight-chain adduct, 1-chloro-1,1,2,2,3,4,4,4-octafluorobutane (I), was separated from a complex reaction mixture by careful fractionation. The isomeric product (Ia) was obtained in only 2% yield.

When chlorodifluoromethane was heated at 210 °C in the presence of tetrafluoroethylene at pressures in the range 1–112 atm, no 1-chloro-1,1,2,2,3,3-hexafluoropropane (IV) was obtained. Cyclic dimerization of the olefin occurred at elevated pressures or temperatures.

Dehydrofluorination of Fluoro Hydrocarbons. Fluorocarbon olefins cannot be made directly from hydrocarbon olefins by treatment with fluorine or a reactive high-valency metal fluoride, since these methods lead to addition of fluorine across C=C bonds. Among the general methods reported for their preparation are dehydrofluorination reactions which are usually achieved thermally,[16] catalytically,[17-24] or by aqueous alkali elimination.[25,26] It seemed feasible to attempt HF elimination by the use of potassium hydroxide under anhydrous conditions. Thus a good yield (93%) of *cis*- and *trans*-1-chloroheptafluorobut-2-ene (Ib) was obtained when I was heated at 60–70 °C in vacuo in the presence of anhydrous, powdered potassium hydroxide (Scheme II). Heating above

Scheme II

I → $CF_2ClCFCFCF_3$ + $CF_2ClCF_2CFCF_2$ (Ib) (cis and trans)

II → Me_3CCFCF_2 (IIb)

III → $Me_3CCFCHF$

IIIa → $Me_3CCFCHF$ + Me_3CCHCF_2 (IIIb + IIIc) (cis and trans)

(KOH, Δ)

Table I. NMR Parameters of the 1:1 Adducts

Compd	Chemical shifts,[a] ppm								Coupling constants, $J_{HF,FF_{gem}}$, Hz			
	δCF_2	δCHF_2	δCHF	δCH_2F	δCF_3	δCHF_2	δCHF	δCH_2F	CHF_2	CHF	CH_2F	CF_2
$Me_3CCHFC-HF_2$		50.0 (d)	130.2 (d)			0.98 (t)	2.69 (d)		50.8	46.2		
$Me_3CCF_2-CH_2F$	42.2			160.4 (t)				2.25 (d)			47.7	
$Me_3CCF_2-CHF_2$	46.4	54.2 (d)				0.81 (t)			53.4			
$CF_2ClCF_2-CHFCF_3$	43.0, 51.0		136.2 (d)		−1.6		1.83 (d)			44.0		284.0

[a] ^{19}F, values to external trifluoroacetic acid; ^1H, positive values to high field of external benzene.

Table II. NMR Parameters of the Fluoro Olefins

Compd	Chemical shifts,[a] ppm								Coupling constants, J, Hz					
	δCF_a	δCF_b	δCF_x	δCF_2	δCF_3	δCH	δCMe_3[e]	J_{HF_a}	J_{HF_b}	$J_{F_aF_b}$	$J_{F_aF_x}$	$J_{F_bF_x}$	$J_{F_aF_y}$	$J_{F_bF_y}$	$J_{F_xF_y}$
$Me_3CCF_b-CHF_a$(cis)	−94.2[c]	−63.4[c]				−0.47[c]	−5.84	74.68	19.74	11.28					
$Me_3CCH-CF_aF_b$	−11.0[e]	−11.0[e]				−0.16	−5.84								
$Me_3CCF_x-CF_aF_b$	−27.8[c]	−43.2[c]	−99.8[c]				−5.14			85.0	45.0	110.0			
$_yF_2CClCF_b-CF_aCF_{3_x}$	−61.0[f]	−68.0[f]		19.0[g]	11.0[h]					8.5	9.59	8.46	5.08	12.69	16.36
$_yF_2CClCF_b-CF_aCF_{3_x}$(trans)	−76.8[f]	−83.0[f]		17.6[g]	7.0[h]					137.6	20.30	7.33	11.28	29.33	1.0

[a] ^{19}F values to external trifluoroacetic acid and ^1H to external benzene. [c] Doublet of doublets. [e] Complex. [f] Doublet of quartets of triplets. [g] Doublet of doublets of quartets. [h] Doublet of doublets of triplets.

70 °C resulted in the formation of undesirable side products. Optimum yield was obtained when a solid–gas phase, rather than solid–liquid phase, was maintained. There was little evidence for the formation of the isomeric olefin, 4-chloroheptafluorobut-1-ene (Ic). The isomeric ratio of Ib was found to be cis:trans, 44:56.

Dehydrofluorination of I with 80% aqueous potassium hydroxide gave only a low yield of the corresponding cis and trans olefins (Ib). The unreacted fluorobutane was difficult to extract from the reaction mixture.

The cis and trans isomers of Ib showed four regions of absorption in their ^{19}F NMR spectra which are presented in Table II.

A good yield (71%) of the isomeric olefins 1,2-difluoro-3,3-dimethylbut-1-ene (*cis*- and *trans*-IIIb) and 1,1-difluoro-3,3-dimethylbut-1-ene (IIIc) was obtained when a mixture of III and IIIa was treated similarly, with dry KOH at 80–85 °C. The major products were the cis isomer of IIIb and IIIc. The trans isomer of IIIb was obtained in small yield.

Above 95 °C considerable charring occurred which decreased the total yield of the fluoro olefins. An increased yield of the cis isomer of IIIb, at the expense of IIIc, was observed at temperatures above 85 °C.

The cis isomer of IIIb showed two regions of absorption in its ^{19}F NMR spectrum, whereas IIIc exhibited only a complex F_aF_b absorption (Table II). The mass spectrum of the cis isomer of IIIb showed significant ions at *m/e* 120 ($C_6H_{10}F_2^+$, 14.2%) and 105 ($C_5H_7F_2^+$, 100%). The most abundant ion at (P − 15) was due to allylic cleavage. This allylic cleavage was also observed in the mass spectra of IIIc and the trans isomer of IIIb.

1,1,2,2-Tetrafluoro-3,3-dimethylbutane (II) was more resistant toward dehydrofluorination than III and IIIa. Therefore a higher temperature and a longer reaction time were necessary. A low (21%) conversion to the corresponding olefin (IIb) together with a small amount of an unidentified product was obtained.

The ^{19}F NMR spectrum (Table II) of IIb showed three regions of absorption. The F_a absorption was broad, probably owing to "through space" coupling with the Me_3C group. Similarly the absorption peak due to the Me_3C group was complex owing to "through space" HF coupling. The mass spectrum of IIb exhibited the most abundant ion in (P − 15) due to allylic cleavage, which is accord with that of IIIc and IIIb. The mass spectrum of the minor reaction product showed *m/e* 120 ($C_6H_{10}F_2^+$, 15.2%) and 105 ($C_5H_7F_2^+$, 100%).

The dehydrofluorination reactions described reveal more about the general characteristics of this type of process for the preparation of fluoro olefins. The results indicate that the ease of dehydrofluorination is I > III ≃ IIIa > II. Compounds III and IIIa form 43% of the cis olefin whereas only 3% of the trans isomer is formed. Along these lines Buxton and Tatlow,[25] in their preparation of pentafluorocyclobutene from hexafluorocyclobutane, report that HF is eliminated preferentially from the two adjacent CHF groups, the flanking CF_2 groups being more resistant to removal of fluorine.

The new fluoro olefins which have been obtained are being currently investigated for their polymerizability.

Experimental Section

NMR spectra were recorded on Perkin-Elmer R10 or R20 spectrometers operating at 60 (^1H) or 56.46 MHz (^{19}F). In certain cases a Varian Associates HA-100 spectrometer operating at 100 (^1H) and 94.12 MHz (^{19}F) was employed. Mass spectra were obtained using an AEI MS 902 double-focusing instrument. Infrared spectra were recorded on Perkin-Elmer spectrophotometers (Models 137 and 257). Volatile samples (gases and liquids with adequate vapor pressures at room temperature) were examined in a gas cell (10-cm path length). A Pye 104 gas–liquid chromatograph was used for the analysis of

liquids. Gaseous mixtures were analyzed on a Perkin-Elmer Model 451. Yields are calculated based on olefins consumed.

Preparation of 1,1,2-Trifluoro-3,3-dimethylbutane (III) and 1,2,2-Trifluoro-3,3-dimethylbutane (IIIa). A. Isobutane (19.2 g, 331 mmol) and trifluoroethylene (9.05 g, 110 mmol) were sealed in vacuo into a 250-ml Hastalloy-lined autoclave and heated with rocking at 280 °C for 96 h. The volatile product was transferred to a conventional vacuum system via an external trap cooled to −78 °C (dry ice–methanol) and distilled in vacuo through traps cooled successively to −23 (CCl_4 slush), −78, and −196 °C. The product which condensed at −196 °C was shown by ir spectroscopy and GLC (using a 2-m dinonyl phthalate column at 60 °C) to be isobutane (15.6 g, 269.5 mmol, 81.2% recovery).

The product which condensed at −78 °C was combined with the contents of the external trap (6.7 g) and fractionated up a Nester-Faust column to give a liquid mixture (0.81 g), bp 40–80 °C (unidentified), a mixture (5.2 g), bp 86–88 °C, of III (2.75 g, 19.6 mmol, 17.8% yield), and IIIa (2.5 g, 17.8 mmol, 15.2% yield), and a higher boiling liquid residue (0.41 g). The high boiling product which remained in the autoclave (5.0 g) was shown by NMR to be telomers and was not examined further.

B. Isobutane (37.9 g, 654 mmol) and trifluoroethylene (19.05 g, 110 mmol) were heated at 280 °C for 96 h in a 250-ml Hastalloy-lined autoclave to give isobutane (32.7 g, 564 mmol, 83.6% recovery), trifluoroethylene (trace amount by GLC), III (4.0 g, 28.5 mmol, 26% yield): NMR (Table I); mass spectrum *m/e* 140 (M^+).

Anal. Calcd for $C_6H_{11}F_3$: C, 51.42; H, 7.85. Found: C, 51.36; H, 7.90.

IIIa (3.2 g, 22.8 mmol, 21% yield): NMR (Table I); mass spectrum *m/e* 140 (M^+).

Anal. Calcd for $C_6H_{11}F_3$: C, 51.42; H, 7.85. Found: C, 51.39; H, 7.80.

A high-boiling autoclave residue (2.4 g, telomers) was also obtained.

Preparation of 1,1,2,2-Tetrafluoro-3,3-dimethylbutane (II). Tetrafluoroethylene (3.3 g, 33 mmol) and isobutane (5.7 g, 99 mmol) were sealed in vacuo into a 3.5-l. Pyrex bulb and heated at 210 °C for 96 h to give isobutane (4.8 g, 86.2 mmol, 84% recovery), tetrafluoroethylene (1.6 g, 16 mmol, 48% recovery), perfluorocyclobutane (0.39 g, 1.98 mmol, 12% yield), and II (1.04 g, 6.6 mmol, 60% yield): bp 83 °C; NMR (Table I); mass spectrum *m/e* 158 (M^+).

Anal. Calcd for $C_6H_{10}F_4$: C, 45.56; H, 6.32. Found: C, 45.60; H, 6.40.

Preparation of 1-Chloro-1,1,2,2,3,4,4,4-octafluorobutane (I). Hexafluoropropene (0.67 g, 4.5 mmol) and chlorodifluoromethane (1.16 g, 13.5 mmol) were sealed in vacuo into a 300-ml Pyrex ampule and heated at 280 °C for 4 days to give hexafluoropropene (0.20 g, 1.4 mmol, 30% recovery), chlorodifluoromethane (1.0 g, 11.7 mmol, 86% recovery), and I (0.32 g, 1.4 mmol, 58% yield): bp 44.5 °C; NMR (Table I); mass spectrum *m/e* 238, 236 (M^+).

Anal. Calcd for C_4HClF_8: C, 20.29; H, 0.42. Found: C, 20.32; H, 0.50.

About 2% of the isomer 1-chloro-1,1,2,3,3-pentafluoro-2-trifluoromethylpropane (Ia) was detected by NMR. Other complex mixtures (0.41 g) were also obtained.

Reaction between Tetrafluoroethylene and Chlorodifluoromethane. Tetrafluoroethylene (10 g, 100 mmol) and chlorodifluoromethane (54.5 g, 630 mmol) were sealed in vacuo into a 250-ml Hastalloy-lined autoclave and heated with rocking at 210 °C for 96 h. The volatile product was transferred to a conventional vacuum system and distilled in vacuo through traps cooled successively to −78, −95 (toluene slush), and −196 °C to give chlorodifluoromethane (quantitative recovery), perfluorocyclobutane (9.2 g, 46 mmol, 92% yield), and a liquid product (trace) which did not appear to be 1-chloro-1,1,2,2,3,3-hexafluoropropane (IV) by GLC–mass spectroscopy (2-m Phasesep at 100–170 °C). No C_2F_4 was recovered.

The above experiment was repeated several times, taking various mole ratios of hydrocarbon to olefin (varying pressures), and in all cases perfluorocyclobutane was obtained as the sole product.

Preparation of 1-Chloroheptafluorobut-2-ene (*cis*- and *trans*-Ib). A. A two-necked round-bottom flask was fitted with a gas inlet tube and a condenser surmounted by a cold-finger condenser and an external trap kept at −78 °C. I (1.1 g, 4.6 mmol) was bubbled in a stream of nitrogen through an excess of 80% (w/v) aqueous potassium hydroxide at about 80 °C contained in the flask. On completion of the addition, the cold finger was allowed to attain room temperature and the apparatus was purged with nitrogen. The organic product collected in the external trap was transferred to a conventional vacuum system. Analysis by ir and GLC (2-m Phasesep at 80–150 °C) confirmed the presence of the cis isomer of Ib (0.11 g, 0.51 mmol, 10% yield) and the trans isomer of Ib (0.12 g, 0.55 mmol, 11% yield). Only a trace amount of I was recovered.

B. I (0.61 g, 2.58 mmol) and anhydrous, powdered potassium hydroxide (6.4 g) were heated in vacuo (150-ml Pyrex ampule) at 60–70 °C for 30 min. It was imperative not to increase the temperature about 70 °C. The volatile product was then transferred to a vacuum system and shown by GLC (2-m Phasesep column at 80–150 °C) to contain I (0.03 g, 0.12 mmol, 4% recovery) and the cis isomer of Ib (0.25 g, 1.15 mmol, 40.9% yield): ir (vapor) 5.58 cm^{-1} (s) (C=C); NMR (Table II); mass spectrum *m/e* (rel intensity) 218 (M^+, 6.3), 216 (M^+, 20.6), 199 (M − F, 5.9), 197 (M − F, 18.9), 181 (M − Cl, 100), 149 (M − CF_3, 28.8), 147 (M − CF_3, 78.5), 131 (M − CF_2Cl, 96.7).

Anal. Calcd for C_4ClF_7: C, 22.22. Found: C, 22.3.

Trans isomer of Ib (0.32 g, 1.48 mmol, 52.1% yield): ir (vapor) 5.79 cm^{-1} (s) (C=C); NMR (Table II); mass spectrum *m/e* (rel intensity) 218 (M^+, 5.6), 216 (M^+, 17.6), 199 (M − F, 3.7), 197 (M − F, 12.2), 181 (M − Cl, 99.7), 149 (M − CF_3, 16.8), 147 (M − CF_3, 51.8), 131 (M − CF_2Cl, 100).

Anal. Calcd for C_4ClF_7: C, 22.22. Found: C, 22.3.

Preparation of 1,2-Difluoro-3,3-dimethylbut-1-ene (IIIb) and 1,1-Difluoro-3,3-dimethylbut-1-ene (IIIc). A mixture of III and IIIa (0.59 g, 4.2 mmol) and anhydrous, powdered potassium hydroxide (12 g) were heated in vacuo (100-ml Pyrex ampule) at 80–85 °C for 90 min. The volatile product was transferred to a vacuum system. This process was repeated three times. The volatile product was then separated by preparative GLC (2-m Phasesep at 150 °C) and shown to contain starting materials III and IIIa (0.15 g, 1.07 mmol, 25% recovery) and IIIc (0.11 g, 0.91 mmol, 25.2% yield): ir (vapor) 3.35 (s) (C–H stretch), 5.75 cm^{-1} (s) (C=C); NMR (Table II); mass spectrum *m/e* (rel intensity) 120 (M^+, 20.5), 105 (M − CH_3, 100), 77 (M − C_3H_7, 31.5), 65 (M − C_4H_7, 19.8), 59 (M − C_3H_6F, 21), 57 (M − C_2HF_2, 6.7).

Anal. Calcd for $C_6H_{10}F_2$: C, 60.0; H, 8.3. Found: C, 60.0; H, 8.2.

Cis isomer of IIIb (0.19 g, 1.5 mmol, 43% yield): ir (vapor) 3.31 (s) (C–H stretch), 5.84 cm^{-1} (s) (C=C); NMR (Table II); mass spectrum *m/e* (rel intensity) 120 (M^+, 14.2), 105 (M − CH_3, 100), 77 (M − C_3H_7, 38.7), 59 (M − C_3H_6F, 9.8), 57 (M − C_2HF_2, 6.6).

Anal. Calcd for $C_6H_{10}F_2$: C, 60.0; H, 8.3. Found: C, 59.9; H, 8.4.

Trans isomer of IIIb (0.013 g, 0.1 mmol, ca. 3% yield): ir (vapor) 3.39 (s) (C–H stretch), 5.70 cm^{-1} (s) (C=C); mass spectrum *m/e* (rel intensity) 120 (M^+, 9.4), 105 (M − CH_3, 3.2), 77 (M − C_3H_7, 21.1), 59 (M − C_3H_6F, 4.2), 57 (M − C_2HF_2, 1.8), 43 (M − $C_4H_{10}F$, 100).

Preparation of 1,1,2-Trifluoro-3-3-dimethylbut-1-ene (IIb). II (1.0 g, 6.38 mmol) and anhydrous, powdered potassium hydroxide (6.55 g) were heated in vacuo at 155 °C for 20 h to give a liquid mixture (0.85 g) which was shown by GLC (using a 2-m Phasesep column at 160 °C or a 2-m dinonyl phthalate column at 60 °C) to contain II (0.62 g, 3.92 mmol, 62% recovery) and IIb (0.18 g, 1.3 mmol, 21% conversion, 54% yield): ir (vapor) 5.65 cm^{-1} (s) (C=C); NMR (Table II); mass spectrum *m/e* (Rel intensity) 138 (M^+, 16.0), 123 (M − CH_3, 100), 95 (M − C_2F, 26.1), 88 (M − CF_2, 10.5), 77 (M − C_3H_6F, 17.4), 73 (M − $C_2H_3F_2$, 23.7), 69 (M − CF_3, 10.4), 59 (M − $C_2H_5F_2$, 26.6), 57 (M − C_2F_3, 13.4), 39 (M − $C_3H_6F_3$, 12.0), 32 (M − $C_5H_8F_2$, 62.0).

Anal. Calcd for $C_6H_9F_3$: C, 52.17; H, 6.52. Found: C, 52.1; H, 6.6.

A product (ca. 0.05 g), mass spectrum *m/e* 120 (M^+), corresponding to $C_6H_{10}F_2$ was also obtained which was not further investigated.

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Registry No.—I, 53005-36-0; *cis*-Ib, 58384-33-1; *trans*-Ib, 58384-34-2; II, 354-75-6; IIb, 58384-35-3; III, 58384-36-4; IIIa, 58384-37-5; *cis*-IIIb, 58384-38-6; *trans*-IIIb, 58384-39-7; IIIc, 58384-40-0; isobutene, 75-28-5; trifluoroethylene, 359-11-5; tetrafluoroethylene, 116-14-3; hexafluoropropene, 116-15-4; chlorodifluoromethane, 75-45-6.

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Organometallic Chemistry. 12. Proton and Carbon-13 Nuclear Magnetic Resonance Study of Arenemercurinium Ions, the Intermediate Complexes of Aromatic Mercuration

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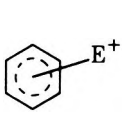
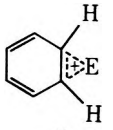
Arenemercurinium ion complexes were prepared and studied by proton and carbon-13 NMR spectroscopy. It is concluded that the complexes are involved in fast exchange.

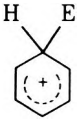
Electrophilic substitution reactions of aromatic compounds proceed via a mechanism involving intermediates of the types **1–3**.[2]



1
Mulliken outer π complex

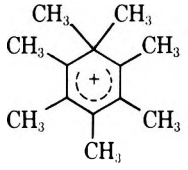


2
π complex (benzonium ion)



3
σ complex (benzenium ion)

Protonated arenes (arenium ions **3**) have been extensively studied,[3] but relatively little information is available regarding intermediates with other electrophiles. The heptamethyl **4** and heptaethylbenzenium ions are known from NMR studies,[4] and also from an x-ray crystallographic investigation of **4**.[5] Recently, direct observation of long-lived σ-complexes in



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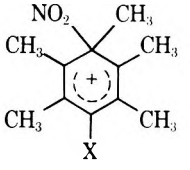

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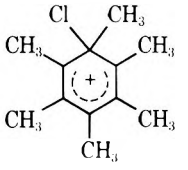


6

nitration[6,7] (**5**) and chlorination[7] (**6**) of hexasubstituted benzenes was also reported.

Although the existence of π-bonded aronium ions **2** is suggested by chemical evidence, they have never been observed as reaction intermediates. We have reported the preparation of bridged π complexes of olefin–mercurinium ions and have investigated them by NMR spectroscopy.[8] We considered, therefore, that a similar study of arenemercurinium ions might yield information on intermediate π-bonded complexes. Previously π-bonded complexes (of type **1**) have been proposed for the mercurinium complexes of hexasubstituted benzenes from ^{1}H NMR studies,[9] while a σ complex was considered consistent with the complicated ^{1}H NMR spectrum obtained for the related pentamethylbenzenemercurinium ion.[9]

We now wish to report the results of our investigations by ^{1}H NMR and ^{13}C NMR spectroscopy of the intermediate complexes in aromatic mercurations.

Results and Discussion

Aromatics were mercurated using either mercuric trifluoroacetate or methylmercury acetate with excess fluorosulfuric acid in SO_2 solution.[9] ^{1}H NMR parameters of the intermediate arenemercurinium complexes so formed are summarized in Table I. In the ^{1}H NMR spectrum of monosubstituted benzenium ion complexes the ortho and meta protons show an AB-type quartet, the meta protons being further split by coupling with the para proton to give a doublet of doublets. Comparable spectra were obtained when *m*-methylanisole, 1,2,4-trimethoxybenzene, and pentamethylbenzene were mercurated. The observed spectra show some similarity to those obtained for monosubstituted ethylenearenium and benzenium ions (Table II).[10] Upon comparison, the ortho and meta protons of the mercurinium ion complexes are slightly shielded, the para proton more so, than the protons of the analogous arenium ions. However, the ^{1}H NMR spectra obtained from the mercurinium ion complexes of benzene, *m*-xylene, mesitylene, and 1,3,5-trimethoxybenzene are similar to those of the uncomplexed parent arenes except that the protons of the former show slight deshielding. No shifts characteristic of benzenium ions were observed.

Table III summarizes the ^{13}C NMR data for the arenemercurinium ion complexes investigated. For the arenemercurinium ions derived from monosubstituted benzenes, the ^{13}C NMR spectra show shifts characteristic of arenium ions. Upon complexation, ipso and ortho carbons become more deshielded, meta carbons are slightly deshielded, whereas shielding is observed for the para carbon. However, the shifts for the mercurinium complexes are not as large as for the corresponding ethylenearenium and arenium ions (Table II). On the other hand, unlike the corresponding arenium ions, the carbon-13 spectra of the mercurinium complexes of benzene, *m*-xylene, and mesitylene show symmetries related to their parent hydrocarbons, but not the arenium ions.

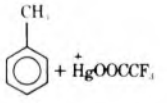
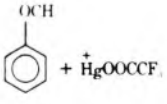
Based on the evidence of chemical shift data alone the possibility of the formation of σ complexes cannot be completely ruled out. The deshielding of the para proton and carbon in the monosubstituted complexes relative to the

Table I. ^{1}H NMR Spectral Data of Arenemercurinium Ions in SO_2 Solution[a]

Arene	Ion registry no.	H_2	H_3	H_4	H_5	H_6	Other protons	Coupling constants, Hz	Temp, °C
Benzene	58747-09-4	8.33 (s)							−60
Toluene	58747-08-3	8.23 (d)	8.73 (dd)	7.47 (t)			CH_3, 3.00 (s)	$J_{2,3}$ = 7.5 $J_{3,4}$ = 5.5	−70
Anisole	58747-07-2	7.44 (d)	8.00 (dd)	7.03 (t)			OCH_3, 4.07 (s)	$J_{2,3}$ = 7.8 $J_{3,4}$ = 6.3	−40
Fluorobenzene	58747-10-7	7.97 (dd)	8.67 (m)	7.23 (um)				J_{H_2-F} = 22.0 $J_{2,3}$ = 8.5	−70
m-Xylene	58747-06-1	7.97 (um)		7.38 (dd)	8.47 (t)		CH_3, 2.77 (s)	$J_{4,5}$ = 6.4 $J_{2,4}$ = 1.4	−60
p-Methylanisole	58747-05-0	7.43 (s)		6.83 (d)	8.10 (dd)	7.32 (d)	CH_3, 2.71 (s) OCH_3, 4.07 (s)	$J_{4,5}$ = 6.0 $J_{5,6}$ = 8.0	−60
Mesitylene (1,3,5-trimethylbenzene)	58747-15-2	7.37 (s)					CH_3, 2.80 (s)		−60
1,3,5-Trimethoxybenzene	58747-13-0	6.03 (s)					OCH_3 3.83 (s)		−40
1,2,4-Trimethoxybenzene	58747-14-1		7.43 (d)	7.33 (d)		7.80 (d)	OCH_3, 4.57 (s, 3 H) OCH_3, 4.60 (s, 6 H)	$J_{5,6}$ = 8.0	−40
1,2,3,4,5-Pentamethylbenzene	58747-12-9					6.63 (s)	CH_3, 2.67 (s, 9 H) CH_3, 2.43 (s, 6 H)		−60

[a] Chemical shifts in δ (ppm) refer to external Me_4Si capillary. The multiplicities are given in parentheses: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; u, unsolved.

Table II. Comparison of the Monosubstituted Arenemercurinium Ion Complexes with the Corresponding Ethylenearenium and Arenium Ions[a,b]

Compd	^{1}H NMR Data			^{13}C NMR Data			
	H_o	H_m	H_p	C_i	C_o	C_m	C_p
	8.23	8.73	7.47	169	135	148	90
	8.48	9.43	5.05	201	139	181	49
	8.05	8.36		183	138	174	64
	7.44	8.00	7.03	193	118	139	105
	7.5 7.8	8.6 9.0	4.5	193	129 123	169 176	42
	7.47	8.12		170	123	174	49

[a] Data of ethylenearenium and arenium ions are obtained from ref 10. [b] o, ortho; m, meta; p, para, i, ispo refer to the substituent.

Table III. ^{13}C NMR Spectral Data of Arenemercurinium Ion Complexes[a,b]

Arene	C_1	C_2	C_3	C_4	C_5	Other carbon
Benzene	133.2					
	(128.6)					
Toluene	168.6	134.8	147.7	90.1		CH_3 24.2
	(137.8)	(129.3)	(128.5)	(125.6)		(21.2)
Anosole	192.6	118.4	139.0	105.2		OCH_3 57.0
	(158.9)	(113.2)	(128.7)	119.8		(54.7)
Fluorobenzene[c]	176.6	123.5	152.2	87.8		
	(163.8)	(114.6)	(130.3)	(124.3)		
m-Xylene	169.6	136.0		106.5	149.7	CH_3 23.0
	(137.5)	(130.1)		(126.4)	(128.3)	
Mesitylene	171.0	116.1				CH_3 22.97
	(137.4)	(127.1)				(21.0)

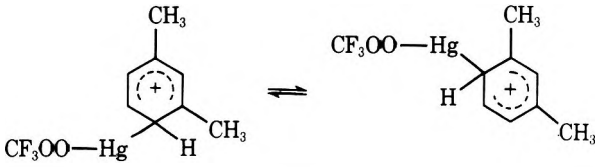
[a] All chemical shifts in δ ^{13}C (ppm) are referred to the external Me_4Si capillary. The chemical shifts of free arene are given in parenthesis for comparison. [b] The complexes generated with $Hg(CF_3COO)_2$ show trifluoromethyl carbon at δ 114.2 (q, J_{C-F} = 283.8 Hz) and carbonyl carbon at δ 161.6 (q, J_{C-C-F} = 42.9 Hz). [c] J_{C_1-F} = 283.5, J_{C_2-F} = 21.8, J_{C_3-F} = 15, and J_{C_4-F} = 0 Hz.

Table IV. J_{C-H} Coupling Constants (Hz) of Benzene, Fluorobenzene, and Mesitylene and Their Mercurinium Ion Complexes

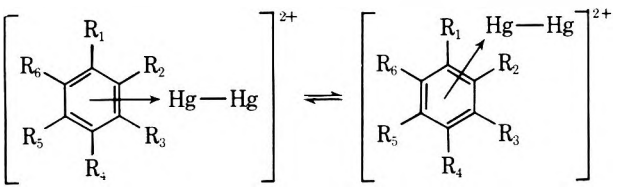
		J_{C-H} (±5 Hz)	
		Parent arene	Mercurinium complex
Benzene		158	172
Mesitylene		154	165
Fluorobenzene	C_o	155[a]	176
	C_m	163	173
	C_p	161	163
Anisole	C_o	159	173[b]
	C_m	159	177
	C_p	162	177

[a] T. F. Page, Jr., *Mol. Phys.*, 13, 523 (1967). [b] Chromium tricarbonyl complex from ref 13.

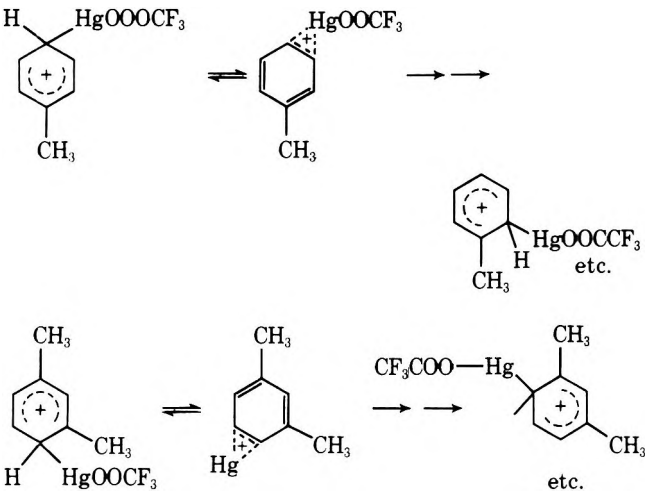
methylene protons and carbon in the corresponding arenium ions could be due to the effect of anistropy of the carbon–mercury bond. The "symmetric" spectra obtained for complexed benzene, *m*-xylene, etc., should then be explained by a fast inter- and/or intramolecular exchange of σ complexes.



However, measurement of J_{C-H} coupling constants should differentiate between the two types of complex. If σ complexes are formed, the J_{C-H} coupling of the carbon at the site of mercuration should show a pronounced decrease in accordance with transformation from sp^2 to sp^3 hybridization. The J_{C-H} coupling constants for the complexes of benzene, fluorobenzene, and mesitylene together with those for the parent arenes and anisolechromium tricarbonyl are given in Table IV. No pronounced decrease of J_{C-H} coupling of the carbon at the site of mercuration upon complexation argues against the formation of σ complexes as the sole stable species observed. Recently a number of arene mercurous complexes were prepared, and the structure of these complexes, in analogy to those of similar argentous complexes, were shown by ^{13}C NMR to be molecularly bonded π complexes with fast bond shifts.[11]



For these complexes both shielded and deshielded shifts (in comparison with the parent substrate) were observed for the ring carbons. Hg_2^{2+} shows a greater deshielding effect, attributed to its greater Lewis acidity compared to Ag^+. The shifts observed for the mercurinium ions of the present study are sufficiently different from those of either the Ag^+ or Hg_2^{2+} complexes, arguing against a similar structure. Furthermore, if the mercurinium complexes were π-bonded Mulliken-type outer complexes or similar to the arene cluster $Cr(CO)_3$ complexes,[12,13] a uniform downfield shift for all carbons relative to the free arene would be expected. This is contrary to what is observed, and thus the present data are inconsistent with the formation of π-bonded arenemercurinium ions. The best description for the arene mercurinium ion complexes is a rapid exchange of σ and π complexes.



Such a rapid exchange is consistent with the reversibility and selectivity of aromatic mercuration reactions. At the same time data do not completely rule out an equilibrating σ-complexed system, in which the π-bridged complexes are only transition states.

Experimental Section

Mercuric trifluoroacetate and methylmercury acetate were purchased from Aldrich Chemical Co., and used without further purification. Fluorosulfuric acid was distilled before use.

Preparation of Complexes. An SO_2 solution at −78 °C of the parent arene was added, with vigorous stirring (vortex mixer), to a SO_2 solution containing excess $(CF_3COO)_2Hg$ or $CH_3COOHgCH_3$ and FSO_3H, also at −78 °C. This solution was then transferred to a precooled NMR probe for examination. Identical NMR spectra were obtained regardless of the other ligand or Hg. However, fluorobenzene was only mercurated by $(CF_3CO0)_2Hg$–FSO_3H.

^1H NMR were recorded on a Varian A56/60 instrument fitted with

a variable temperature probe. ^{13}C NMR were recorded on a Varian XL-100 instrument fitted with a broad band decompling and variable temperature probe.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No.—Benzene, 71-43-2; toluene, 108-88-3; anisole, 100-66-3; fluorobenzene, 462-06-6; *m*-xylene, 108-38-3; *p*-methylanisole, 104-93-8; mesitylene, 108-67-8; 1,3,5-trimethoxybenzene, 621-23-8; 1,2,4-trimethoxybenzene, 135-77-3; 1,2,3,4,5-pentamethylbenzene, 700-12-9; mercuric trifluoroacetate, 13257-51-7; methylmercury acetate, 108-07-6; fluorosulfuric acid, 7789-21-1.

Supplementary Material Available. ^{1}H NMR spectra of anisole- and *m*-xylenemercurinium ions and ^{13}C NMR spectra of fluorobenzene- and anisolemercurinium ions (4 pages). For simplicity signals due to the counteranion were deleted. Ordering information is given on any current masthead page.

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Consecutive Decomposition Modes for *m*-Trifluoromethylphenylcopper in Ether[1]

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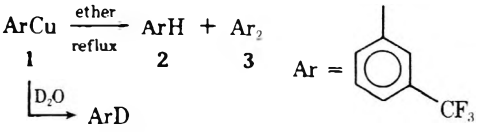
The decomposition of *m*-trifluoromethylphenylcopper in refluxing ether, both in the absence and presence of benzalacetophenone, has been monitored by withdrawing samples from time to time and quenching with D_2O. During the first phase of the decomposition, 3,3′-bis(trifluoromethyl)biphenyl (biaryl) is produced in both cases and, in the presence of the enone, conjugate addition occurs as well; this is the first reported case of a simple conjugate addition of an organocopper in the absence of lithium or magnesium salts. When approximately one-half of the organocopper has been consumed, the above behavior ceases and the remainder of the organocopper is converted to benzotrifluoride by removal of hydrogen from the solvent; such hydrogen removal was demonstrated by performing the decomposition in perdeuteriotetrahydrofuran and noting that the benzotrifluoride produced was monodeuterated to the extent of 46%. It is believed that the organocopper exists in these solvents as a cluster compound which splits out aryl groups pairwise, in competition with conjugate addition, until an intermediate such as Ar_4Cu_8 is reached; the latter then reacts with solvent by one of a number of possible mechanisms, which are discussed.

Results

While attempting to study one aspect of the mechanism of the Ullmann biaryl synthesis,[2] we made the intriguing observation that during the course of decomposition of *m*-trifluoromethylphenylcopper (**1**)[3] in ether solvents, the nature of the process changes markedly from the beginning to the end of the reaction. If this decomposition is carried out in refluxing ether and samples are withdrawn and quenched with water at various times, the quantities of benzotrifluoride (**2**, arene) in the quenched samples decrease and those of 3,3′-bis(trifluoromethyl)biphenyl (**3**, biaryl) increase until after about 6 h when the quantities of the two compounds cease changing.

However, it was soon found that those deceptively simple results mask quite surprising changes in the course of the reaction which start at about the time the quantities of products in the quenched samples become constant. This was ascertained by repeating the reaction, quenching the withdrawn samples with D_2O, and determining the yields in the quenched samples of biaryl (**3**) and arene (**2**) as well as the deuterium content of the latter (by combined gas chromatography–mass spectrometry); this procedure allows a distinction to be made between benzotrifluoride (ArH) which is present in the unquenched sample and that (ArD) which arises upon quenching the reaction mixture, presumably by protonation of an organocopper compound.



The first three columns of Table I indicate the raw data from such an experiment. The zero hour sample was withdrawn as soon as possible after the ether solution of arylcopper (**1**) and the gas chromatographic standard, durene, was removed from the glove box[4] in which it was prepared and before heat was applied. It is again seen that during the interval between 5 and 20 h, the quantities of biaryl and arene in the quenched samples become constant but that a substantial percent of the arene is monodeuterated and is thus derived from unreacted arylcopper; that is to say, even though reaction appears to cease some time between 5 and 20 h, a large amount of the arylcopper is still present. The fourth column indicates that, although there are some fluctuations in our material balance, owing mainly to the difficulty in sampling a mixture that becomes heterogeneous after a few hours (see below), the

Table I. Decomposition of *m*-Trifluoromethylphenylcopper in Refluxing Ether[a]

Time, h	Quantities present in quenched samples, mmol[b] Ar_2[c]	Arene[d] (% D)	Total[e]	Derived quantities, mmol ArCu present	ArH present	Ar_2 formed[f]
0	0.08	1.56 (83)	1.72	1.29	0.27	0
2.5	0.22	1.50 (74)	1.94	1.11	0.39	0.14
5.0	0.40	0.91 (64)	1.71	0.58	0.33	0.32
20.0	0.57	0.84 (30)	1.98	0.25	0.59	0.49
47.5	0.54	0.89 (1)	1.97	0.01	0.88	0.46
77	0.53	0.95 (0)	2.01	0	0.95	0.45
120	0.55	0.93 (0)	2.03	0	0.93	0.47

[a] Solutions were prepared by dissolving 500 mg of *m*-trifluoromethylphenylcopper in 35 ml of ether. [b] Quantities determined by gas chromatography utilizing as an internal standard durene, which was present during the reaction. [c] Ar = *m*-$CF_3C_6H_4$. [d] Benzotrifluoride. [e] mmol arene + 2 (mmol biaryl). [f] After the zero time sample was withdrawn.

total quantity of aryl groups accounted for remains reasonably constant. The quantity of arylcopper present at each time is simply derived by multiplying the total quantity of arene in the quenched samples by the fraction ArD; these quantities are in the fifth column of Table I. The quantity of arene which is present at any time in the reaction mixture before quenching is then the total arene after quenching minus the quantity of arylcopper present and these quantities are in column 6. In the last column, the yields of biaryl (**3**) at various times are listed; they are calculated by subtracting the small quantity (0.08 mmol) of biaryl which is present as a contaminant when the arylcopper is first dissolved in the ether from the quantity of biaryl present at each time. Some arene (0.27 mmol) is present soon after the arylcopper is dissolved in the ether; a part of this may have been present as a contaminant in our sample of arylcopper, which was somewhat tacky, and the remainder may be formed by protolysis of the arylcopper by traces of moisture in the system.

The most striking feature of Table I is the fact that the formation of biaryl essentially ceases some time between 5 and 20 h, long before all of the arylcopper is consumed. The remaining arylcopper is thenceforth converted slowly to arene (**2**).

Organocopper(I) compounds frequently add to enones[5–7] although attempts to add 1 mol of an arylcopper to an enone in the absence of lithium or magnesium halides have heretofore resulted in failure.[5,6,8–10] Nevertheless, we have found that *m*-trifluoromethylphenylcopper does add to an excess of benzalacetophenone in ether solution in competition with self-coupling. When this reaction was monitored as in the previous case, the reaction course was found to be quite analogous to that without added benzalacetophenone. The results of this experiment (Table II), and two similar ones (one of them using aqueous DCl instead of D_2O alone as the quench), which exhibited the same behavior pattern, clearly indicate that conventional organocopper behavior is manifested for less than 20 h; that is to say, the yields of biaryl and conjugate addition product (**4**) remain constant after 20 h. On the other hand, unconventional behavior, the conversion to arene, does not occur to any appreciable extent until toward the end of the 20-h interval, but this reaction is essentially the only one undergone by the organocopper after 20 h. Furthermore, at the end of 20.5 h, the biaryl (**3**) and benzalacetophenone addition product (**4**) account for almost one-half of the 1.53 mmol of arylcopper present at time zero (2 × 0.25 mmol of biaryl + 0.21 mmol of addition product = 0.71 mmol).

$$\underset{\mathbf{1}}{ArCu} + PhCH{=}CHCOPh \xrightarrow{ether} \underset{\mathbf{2}}{ArH} + \underset{\mathbf{3}}{Ar_2} + \underset{\mathbf{4}}{Ph(Ar)CH{-}CH_2COPh}$$

Since completely deuterated diethyl ether was unavailable to us, the source of the hydrogen which replaces the metal was probed by performing the decomposition of *m*-trifluoromethylphenylcopper (**1**) in refluxing perdeuteriotetrahydrofuran. Preliminary experiments in undeuterated THF using D_2O quenches established that at this higher temperature, the reaction proceeded more rapidly and that the final ratio (0.34) of arene to biaryl was far lower than that (1.7) in the ether experiment, but that the broad features of the reaction were the same; biaryl production virtually ceased before the arylcopper was consumed and after that point arene production was essentially the only reaction occurring. Because of the expense of perdeuteriotetrahydrofuran, the decomposition was performed on a far smaller scale than those in the above experiments and the solution was more concentrated. After the organometallic had been dissolved in the solvent and the solution removed from the glove box, a sample was withdrawn and quenched with D_2O to produce benzotrifluoride (**2**) with an ArD content of 76%; thus, the quantity of benzotrifluoride present at zero time was somewhat higher than those of the previous experiments (for example, in a small-scale experiment in THF, 90% of the arene produced upon quenching the zero time sample with D_2O was monodeuterated; see also Tables I and II); this is probably due to the presence of more moisture in the labeled THF which was used directly from the ampule in which it was supplied. The reaction was followed by quenching withdrawn samples with H_2O. The ArD content of the benzotrifluoride produced when reaction was complete was 46%. Although the small quantities used in this experiment precluded an accurate estimate of the

Table II. Decomposition of *m*-Trifluoromethylphenylcopper in the Presence of Benzalacetophenone in Refluxing Ether[a]

Time, h	Compounds present in quenched samples, mmol[b] Ar_2[c]	Arene[d] (% D)	Addn product[e]	Total[f]	Derived quantities, mmol ArCu present	ArH present	Ar_2 formed[g]
0	0.08	1.79 (85)	0	1.95	1.53	0.26	0
2.5	0.17	1.36 (81)	0.13	1.82	1.10	0.25	0.09
5.0	0.25	1.04 (78)	0.17	1.71	0.81	0.23	0.17
20.5	0.33	0.82 (66)	0.21	1.69	0.54	0.28	0.25
46	0.34	0.80 (30)	0.22	1.70	0.24	0.56	0.26
79	0.34	0.85 (2)	0.20	1.73	0.02	0.83	0.26
116	0.31	0.68 (0)[h]	0.23	1.53	0	0.68[h]	0.23

[a–d] As in Table I. [e] 1,3-Diphenyl-3-(*m*-trifluoromethylphenyl)propanone (**4**). [f] mmol arene + mmol 4 + 2 (mmol biaryl). [g] After the zero time sample was withdrawn. [h] Arene lost owing to evaporation during the long heating period.

percent conversion to benzotrifluoride of the arylcopper present at time zero, one can be confident that most, if not all, of the benzotrifluoride produced after time zero resulted from deuterium transfer from the solvent to the aryl groups since the 54% of undeuterated arene present at the end of the reaction can easily be accounted for as that which was present at time zero, presumably from hydrolysis of the organocopper. In fact, it can be calculated that if the percent conversion to arene of arylcopper present at time zero in the labeled THF were the same as that (10.4%) in the large scale more dilute run using predried THF, the percent ArD in the benzotrifluoride would be only 25%;[11] it thus appears that somewhat more arene and less biaryl result from decomposition of the arylcopper in the isotopic experiment.

Some interesting visual observations were made during the course of all the reactions described above. The original brownish black solution turned green after about 2 h (in the ether runs) and, after about 1 h further, copper plating was observed. After about 2 h more, a brown precipitate began to form.

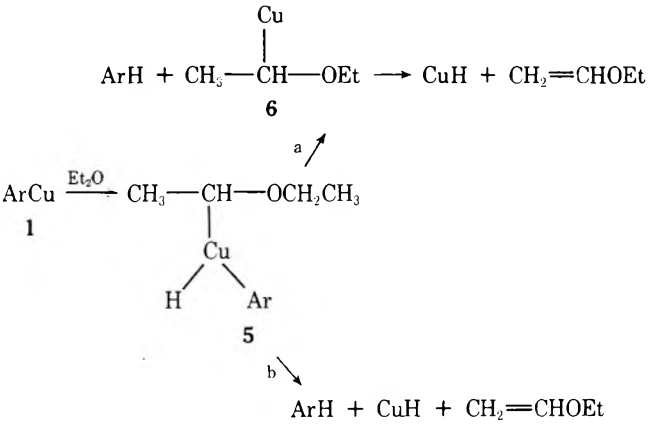
Discussion

As part of their elegant work on the structures and self-coupling reactions of fluorinated arylcoppers, Cairncross and Sheppard[3] made the fascinating observation that *m*-trifluoromethylphenylcopper (1), which is octameric in benzene solution, undergoes pairwise loss of aryl groups in the form of biaryl (3) and that metallic copper does not appear until about one-half of the arylcopper is decomposed to biaryl. Furthermore, they were able to isolate the green intermediate Ar_6Cu_8. Eventually, virtually all of the arylcopper is converted to biaryl.

$$Ar_8Cu_8 \longrightarrow Ar_2 + Ar_6Cu_8 \longrightarrow$$
$$Ar_2 + Ar_4Cu_8 \longrightarrow 2Ar_2 + 8Cu$$

Their discovery provides an excellent basis for a rationalization of our own otherwise bewildering results. It appears likely that the cluster compound which exists in ether also splits out biaryl stepwise in competition with adding to benzalacetophenone, when the latter is present. However, some intermediate, present when about one-half of the aryl groups have been consumed (Ar_4Cu_8 if the original compound is octameric in ether), decomposes in a different way to yield arene by interaction with the solvent. The green color which develops fairly early in our decomposition reactions may very well correspond to the complex Ar_6Cu_8 isolated by Cairncross and Sheppard.[3] This finding is a rather remarkable demonstration of the different behavior of which arylcoppers in different states are capable and it suggests possibly interesting properties or organocopper compounds in which the average oxidation level of the metal is between 0 and 1.

Four different general modes of transfer of hydrogen from the ether solvent to the aryl group can be envisioned. (1) A proton abstraction by the arylcopper appears somewhat unlikely in view of the finding by Whitesides (footnote 21 of ref 12) that alkylcoppers are not sufficiently basic to abstract protons from diethyl ether; alkylcoppers would be expected to be far more basic than arylcoppers. However, this route cannot be completely ruled out since our present state of knowledge about species such as Ar_4Cu_8 is negligible. (2) Abstraction of hydrogen from the ether by nascent copper and subsequent reaction of the copper hydride with the arylcopper. An analogy for the last step is available from the work of Whitesides et al. on the decomposition of alkylcoppers.[13] However, we know of no precedents in copper chemistry for the hydrogen removal step, although Tamura and Kochi,[14] in order to account for the production of excess alkane during decomposition of alkylmanganese compounds, have speculated that an active form of manganese may be capable of dehydrogenating THF to form a manganese hydride. (3) An oxidative addition of a CH bond of the ether to the arylcopper(I) could provide an arylcopper(III) hydride (5) which, by reductive elimination (path a), could yield arene and an organocopper (6).[15,16] Another mole of arene would then be produced by reaction of the arylcopper with copper hydride which would readily be lost from 6. Alternatively, the same



products could be formed from 5 by heterolytic cleavage of the bond between the ether moiety and copper (path b) with either concerted abstraction of the β proton by the aryl group (oxidative elimination[17]) or formation of a carbonium ion (oxidative solvolysis[17]) and subsequent abstraction of the β proton. The oxidative addition of alkyl and aryl CH bonds to various transition metals has ample precedent.[18] (4) The form of organocopper present during the latter part of the reaction may decompose to aryl radicals which can abstract hydrogen atoms from the ether. The α-CH bonds of ethers are quite labile toward hydrogen atom removal.[19] While Cairncross and Sheppard[3] found no evidence for attack of aryl radicals on the benzene solvent during the decomposition of *m*-trifluoromethylphenylcopper, it may be either that coordination of ether with the organometallic changes the reactivity pattern or that the formation of radicals is reversible and that if no particularly low energy reaction path is available to the aryl radicals, they recombine with copper leading eventually to biaryl. A number of examples are available of radical decomposition of alkylcoppers and in several cases the alkyl radicals remove hydrogen atoms from the ether solvent;[20] this mode of decomposition is particularly prevalent in the case of alkylcoppers lacking β-hydrogen atoms, although the possibility has recently been raised that alkylcoppers in general may decompose by a radical pathway.[21] The radical pathway 4 has the best precedents but pathway 3 is more consistent with the apparent absence of aryl radicals during the decomposition of 1 in benzene.

In summary, a cluster compound of *m*-trifluoromethylphenylcopper appears to lose aryl groups by self-coupling and by conjugate addition to an enone until an intermediate species is reached. The latter organometallic does not undergo the above reactions but instead a hydrogen of the ether solvent replaces the copper to form benzotrifluoride; further work would be required to elucidate the nature of this latter reaction. This work provides the first example of the simple conjugate addition of an organocopper in the absence of lithium or magnesium salts.

Experimental Section

General. Routine infrared spectra were taken on a Beckman IR-8 spectrophotometer; when spectra were needed below 625 cm^{-1}, a Beckman IR-10 or IR-12 spectrophotometer was used. Nuclear magnetic resonance spectra were determined on a Varian T-60 spectrometer. Chemical shift data are reported in δ (ppm) units relative to tetramethylsilane. For purity checks on deuterated reagents, weighed amounts of 1,4-dioxane or chloroform were used as appro-

priate standards. Mass spectra were recorded on a LKB-9000 combined gas chromatograph–mass spectrometer; high-resolution mass spectra were determined on an AEI MS-9 spectrometer using a direct insertion probe at 70 eV.

Gas–liquid partition chromatographic (GLC) analyses were performed on a Hewlett-Packard 5750 gas chromatograph using a Disc Instruments No. 229 Series D Disc chart integrator or on a Varian Aerograph 1860-3 gas chromatograph with a No. 204 Disc chart integrator. These instruments were equipped with flame ionization detectors. Stainless steel columns (10 ft × 0.125 in.) were used. The flow rate of air was approximately 360 ml/min and of hydrogen about 52 ml/min; nitrogen carrier gas flow rates (ml/min) were 50 for the 3% OV-17 on 100/120 mesh Gas Chrom Q (column A), 22 for the 10% Carbowax 20M on 60/80 mesh Chromosorb W (B), and 47 for the 3% OV-225 on 100/120 mesh Gas Chrom Q (C). Absolute yields were calculated from peak areas using durene as internal standard. Calibration curves of three points were constructed utilizing flame response factors obtained with authentic samples. The identities of all reaction products of which authentic samples were available were checked by comparison of their retention times by coinjection on two GLC columns as well as of their mass spectra.

The percent of monodeuteriobenzotrifluoride in labeled samples of arene was determined from the relative peak heights[22] in the combined GLC–mass spectrogram at 15 eV utilizing column B.

Drybox work was performed in a Labconco fiberglass controlled atmosphere glove box. The prepurified nitrogen was passed through a tube of copper turnings, heated (450 °C) in a tube furnace, and a column of Drierite. The usual precautions for handling air and moisture sensitive organometallic compounds were observed.[23] The apparatus in which the organocopper was used was assembled and charged with the reagents in the glove box and was then removed to the bench where the dry nitrogen atmosphere was maintained.

Reagents and Solvents. Durene, m-iodobenzotrifluoride, magnesium, and tetrahydrofuran-d_8 (Norell Chemical Co.) were used directly as obtained from commercial sources. m-Bromobenzotrifluoride (Pierce Chemical Co.) was also used as supplied; it is known to contain ca. 2% of the para isomer which cannot be removed by distillation through a spinning band column.[26] Benzalacetophenone (chalcone, Eastman and J. T. Baker) was recrystallized from ethanol, mp 59.0–59.5 °C. Copper powder (Valimet 1107, formerly Englehard Magna 1107) was activated[28] with 0.24 M aqueous ammonia. 1,4-Dioxane was heated at reflux over lithium aluminum hydride, distilled at 101 °C, and stored under nitrogen over 5A molecular sieves. Deuterium chloride solution was prepared by adding deuterium oxide to benzoyl chloride (1:2 mole ratio) and distilling under nitrogen. Deuterium oxide-d_2 (Stohler Isotope Chemicals, 99.8% D) purity checks (NMR vs. dioxane standard) were performed on various bottles and ranged from 99.2 to 99.9% D. Diethyl ether (J. T. Baker, anhydrous reagent), was heated at reflux over lithium aluminum hydride for several hours and distilled under nitrogen. Tetrahydrofuran (Fisher certified) was heated at reflux with lithium aluminum hydride for several hours, distilled under nitrogen, bp 66 °C, and stored in the drybox for use in organocopper reactions.

3,3'-Bis(trifluoromethyl)biphenyl (3). This compound was prepared by an Ullmann coupling of m-iodobenzotrifluoride according to the procedure of Petit and Tatlow.[24] The product distilled at atmospheric pressure at 242.0–243.5 °C (lit.[24] bp 237–240 °C). GLC analysis indicated greater than 99% purity: NMR (CCl_4) 7.5–7.8 ppm (m); ir 1343, 1325, 1306, 1253, 1168, 1130, 1099, 1078, 1047, 795, and 702 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 291 [16, $(P + 1)^+$], 290 (base, P^+), 271 (15, $P^+ - F$), 207 (20), 206 (19), 205 (21), 179 (68), 177 (72), 145 (8, $C_{14}H_8F_6^{2+}$ or $C_7H_4F_3^+$), 99 (11), 74 (13), 59 (20).

3-(m-Trifluoromethylphenyl)-3-phenylpropiophenone (4). This compound was prepared by the method used by Holmberg and Axberg[25] to prepare 3,3-diphenylpropiophenone. A solution of 5.20 g (25.0 mmol) of benzalacetophenone in dry ether (40 ml) was added dropwise during 50 min to the Grignard reagent prepared from 1.41 g (62.5 mmol) of m-bromobenzotrifluoride, and 1.50 g (61.8 mmol) of magnesium in 30 ml of dry ether. The addition rate was controlled so as to maintain the mixture at reflux (34–36 °C) and the mixture was heated at reflux for an additional 20 min. The reaction products were poured into a mixture of ice water and hydrochloric acid and the resulting mixture was extracted with ether. The ether extract was washed with saturated solutions of sodium bicarbonate and sodium chloride. Concentration of the dried ether extract gave a brown oil which was twice recrystallized from ethanol–benzene (5:3) to give a tan solid: mp 60.7–62.0 °C; ir (CCl_4) 3100–3030 (ArCH), 1690 (C=O), 1330 (CF_3), 1130 cm^{-1}; NMR (CCl_4) δ 6.8 (m, ArH), 4.9 (t, CH), and 3.7 ppm (d, CH_2); mass spectrum (70 eV) m/e (rel intensity) 354 (24, P^+), 336 (11), 335 (10, $P^+ - F$), 236 (10), 235 (63, $C_6H_5C^+HC_6H_4CF_3$), 171 (10), 166 (16), 165 (23), 106 (25), 105 (base, $C_6H_5CO^+$), 77 (80, $C_6H_5^+$), 51 (10); high-resolution mass spectrometric molecular weight calcd for $C_{22}H_{17}F_3O$, 354.1231; found, 354.1224.

m-Trifluoromethylphenylcopper (1). The compound was prepared according to the method of Cairncross and Sheppard.[3,26] A four-neck 100-ml round-bottom flask was fitted with a condenser with nitrogen inlet, a thermometer, a dropping funnel with pressure equalizing arm, and a filtering assembly consisting of a medium sintered glass filter followed by an adapter to a vacuum stopcock leading to a one-neck O-ring receiving flask.

After magnesium (0.97 g, 40 mmol) had been charged to the flask, the oven-dried assembled apparatus was further dried by flame while being purged with nitrogen; a solution of 9.0 g (40 mmol) of m-bromobenzotrifluoride in 40 ml of anhydrous distilled ether was added dropwise during 0.5–0.75 h to the magnesium with magnetic stirring at a rate which allowed the mixture to reflux gently. The mixture was heated at reflux for a total time of 1 h from the start of the addition and then cooled to 0 °C. A solid addition tube containing 6.3 g (44 mmol) of purified copper(I) bromide[27] was substituted for the thermometer under increased nitrogen flow; the contents were added in portions in a few minutes. After being stirred for 0.5 h at 0 °C, the mixture was slowly treated over 0.75 h with 15 ml of dry distilled dioxane, and enough cold ether was added to fill the flask (ca. 40 ml). The mixture was filtered in vacuo by inverting the entire apparatus while the filter assembly and receiving flask were being cooled. The solid was washed with an ice-cold solution of ether (40 ml) and dioxane (5 ml) in three portions over 1–1.5 h.

The filtrate was evaporated first on a flash evaporator using a Sargent-Welch Duo-Seal pump (no. 1399) with two traps in Dewar flasks filled with liquid nitrogen. When the distillation flask was cooled in slush baths of 2-propanol/dry ice and 1,2-dichloroethane/liquid nitrogen (−35°), 0.6–2.0 mm pressure was obtained and the bulk of the solvent was stripped off in 3–4 h. The last 10 ml of solvent, including dioxane, was removed on a vacuum line at ca. 10^{-5} mm using successively the above two slushes followed by an ice bath for 4 h to yield a sticky, brownish black solid. The evacuated flask was taken into the glove box and the contents packed as weighed samples (usually 0.50 g) in vials sealed with Parafilm and stored in a closed jar in a Dewar flask of dry ice. Samples were removed for use singly by removing a vial from the jar in a nitrogen-filled glove bag, then quickly returning the jar of samples to the Dewar. The best yield was 52% but not all the mass of solid could be scraped from the flask. The product was characterized and its purity determined in the following manner. A sample of m-trifluoromethylphenylcopper, which had been stored (−78 °C) for 6 months, was dissolved in dry ether and treated with deuterium oxide in a glove bag under nitrogen. The dried ether extract was analyzed by combined GLC–mass spectrometry. By far the major peak was deuteriobenzotrifluoride: MS (15 eV) m/e 148 (7.7), 147 (base, $DC_6H_4CF_3^-$), 146 (7.7). The arene was calculated[22] to be 98% monodeuterated. The gas chromatogram also showed that the arylcopper was contaminated with a few percent of dioxane, and minute traces of m-bromobenzotrifluoride, a chlorobenzotrifluoride, and biaryl; all were identified by mass spectrometry.

Some dry m-$CF_3C_6H_4Cu$ was exposed to air upon which the brownish black solid was transformed to green crystals. Anal. (Alfred Bernhardt) Cu, 36.03; Mg, 0.0 (limit 0.2%). The Cu/Mg atomic ratio is at least 70/1; Cairncross[26a] found 101/1, 117/1.

The infrared spectrum of 1 in the 2000–200-cm^{-1} region was determined as follows. By the use of Nujol which had been deoxygenated by passing nitrogen through it, a sample of $(m\text{-}CF_3C_6H_4)_8Cu_8$ of known high purity was mulled in a glove box between KBr plates; the edges of the plates were wrapped with Parafilm. The sample was placed in a desiccator along with a sample mulled between polypropylene plates similarly wrapped. The spectra of both samples were determined as soon as possible with a nitrogen atmosphere in the sample compartment. The polypropylene plates were used in the ranges 95–260 cm^{-1} (Beckman IR-11) and 200–400 cm^{-1} (Beckman IR-12); the KBr plates were used in the range 400–2000 cm^{-1} (Beckman IR-12). Spectrum: 1583 (m), 1456 (s), 1446 (sh), 1366 (m), 1348 (sh), 1324 (s), 1309 (s), 1179 (sh), 1140 (s,br), 1130 (sh), 1095 (s), 1082 (s), 1049 (s), 992 (m), 933 (m), 897 (m), 892 (m), 878 (m), 874 (sh), 864 (sh), 797 (s), 706 (m), 678 (s), 666 (m), 642 (m), 614 (m), 344, 278 cm^{-1}.

Decomposition of m-Trifluoromethylphenylcopper in the Absence and Presence of Benzalacetophenone in Ether. Initial exploratory experiments were performed with solutions of the organocopper and benzalacetophenone in ether. Samples were withdrawn from time to time and quenched with H_2O or D_2O. The final quantitative reactions were performed as follows. In a glove box, a 50-ml three-neck flask equipped with a serum cap, a condenser mounted

with a gas inlet tube containing a stopcock, and, in those experiments with benzalacetophenone, an addition funnel was charged with 500 mg (2.40 mmol) of 1 and a solution of 67.2 mg (0.500 mmol) of durene in 35 ml of ether. The flask was removed from the glove box but maintained under a nitrogen atmosphere, magnetic stirring was started, and the first 1.5-ml sample was withdrawn by syringe through the septum. The solution was heated to reflux, when the timing began. Other 1.5-ml samples were withdrawn from time to time. Each sample was injected into 2 ml of ice-cold D_2O, and the mixture was stirred for 15 min under nitrogen and extracted with four 6–8-ml portions of ether. The dried (magnesium sulfate) ether extract was stored in capped vials at −20 °C within a closed jar containing Drierite. The visually observed changes which occurred during the reaction are described in the Results. The same procedure was used for the decompositions in the presence of benzalacetophenone, except that an ethereal solution of 2.00 g (9.60 mmol) of the latter was added by the addition funnel; the total volume of ether was also 35 ml. The experiment was done in triplicate; in one run, DCl in D_2O was used for the quench and it was necessary to wash the ether extracts with aqueous sodium bicarbonate and saturated saline solution before drying.

Decomposition of 1 in Tetrahydrofuran. The large-scale run was performed in the same manner as that in ether except that 35 ml of THF was used instead of the ether. The zero hour sample contained 0.10 mmol of biaryl and 1.98 mmol of arene which contained 92% ArD. The following are the results of analyses of samples withdrawn at the stated times after refluxing commenced [time, mmol of biaryl, mmol of arene (% ArD)]: 0.5 h, 0.24, 1.57 (89%); 1.5 h, 0.49, 1.33 (85%); 3 h, 0.97, 0.35 (41%); 18.5 h, 1.01, 0.31 (0%); 45 h, 1.05, 0.34 (0%). The small-scale runs in THF and perdeuterio-THF were performed in similar fashion except that 27 mg (0.20 mmol) of durene, 100 mg (0.48 mmol) of arylcopper, and 2 g of THF were used. In the experiment with unlabeled solvent, D_2O quenches were used. In the experiment with labeled solvent, the zero hour sample (0.3 ml) was quenched with D_2O and subsequent samples with H_2O. Extractions of the quenched samples were performed in centrifuge tubes, with centrifugation being used to break the emulsions. The yields of products were somewhat erratic but, in general, the usual trends were observed. In the labeled case, the zero hour sample contained arene which was 76% monodeuterated and the 3-, 5.5-, and 18-h samples were 43, 46, and 46% monodeuterated, respectively.

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Methanolysis Products of Dichloro(1,5-cyclooctadiene)palladium(II) in the Presence of Bases and of Its Methoxy Adducts[1]

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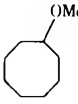
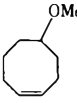
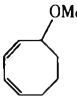
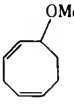
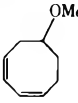
When di-μ-chloro- and di-μ-methoxidobis(2-methoxycyclooct-5-enyl)dipalladium(II) were refluxed in methanol with and without added bases and when dichloro(1,5-cyclooctadiene)palladium(II) was refluxed in methanol with added bases, complex mixtures of products were obtained comprising 4-cyclooctenyl methyl ether and 2,4-, 2,5-, 3,5-, and 1,5-cyclooctadienyl methyl ethers as well as 4-cyclooctenone. Products were identified, and mechanisms are discussed.

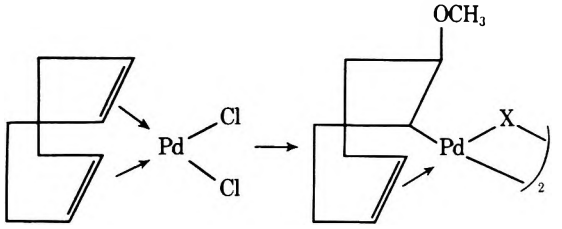
Dichloro(1,5-cyclooctadiene)palladium(II) (1) and the methoxy adduct derived from it, di-μ-chlorobis(2-methoxycyclooct-5-enyl)dipalladium(II) (2-Cl), were reported by Chatt and Vallarino in 1957.[2] Although many other adducts of 1,5-cyclooctadiene have been made and some of their reactions studied,[3] the nature of the organic oxidation products has been given only scant attention.[4] In this report the complex mixtures of organic oxidation products formed when dichloro(1,5-

Table I. Percentage Yield of Products from Methanolysis of (Cyclooctadiene)palladium chloride (1), Di-μ-chlorobis(2-methoxycyclooct-5-enyl)dipalladium(II) (2-Cl), and Di-μ-methoxidobis(2-methoxycyclooct-5-enyl)dipalladium(II) (2-OMe) in Refluxing Methanol (68 °C)[a]

Reaction conditions: compd (mmol), base (mmol), reaction duration, h									Total organic	Total Pd	COD–$PdCl_2$ recovered
2-Cl (0.94), none 5	12.4 (23.3)	<0.1	1.6 (3.0)	0.8 (1.5)	1.8 (3.4)	6.4 (11.8)	1.8 (3.4)	22.3 (51.2)	52.1 (97.6)	53.4 (98.5)	44.6
2-Cl (0.91), Na_2CO_3 (9.4) 5	4.1	0	39.2	14.7	27.3	11.2	0.1	5.1	96.6	99.0	0
2-OMe (0.81), none 1	6.9	<0.1	43.6	22.0	15.4	5.5	0	6.4	99.8	97.5	0
1 (2.44), Na_2CO_3 (3.05) 5	2.7 (4.2)	0.6 (0.9)	15.5 (23.3)	5.7 (8.6)	10.8 (16.3)	13.2 (20.3)	0.2 (0.3)	12.8[b] (19.4)	61.5	66.0	34.0
1 (2.03), Na_2CO_3 (9.4) 3	4.3	0	36.8	11.5	18.5	16.4	<0.1	12.0[b]	99.0	100.0	0
1 (3.36), NaOMe (3.5) 1	7.4	0.7	52.3[c]	18.7	9.5	4.7	0	6.4	99.7	99.0	0
1 (3.4), NaOMe (3.5) 2	<0.1	<0.1	40.0	56.0	<0.1	<0.1	<0.1	<0.1	96.0	100.0	0
1 (2.0), NaOMe (4.1) 1	1.1	1.2	55.8	27.3	8.4	2.8	0	3.2	99.8	98.5	0
1 (1.95), NaOMe (5.9) 1	0	1.6	60.4	36.3	1.6	<0.1	0	<0.1	99.9	97.5	0
1 (2.2), NaOMe (8.7) 1	0	0.2	58.0	41.0	0.3	0.3	0	<0.1	99.7	100.0	0

[a] All reaction solutions were in 15 ml of MeOH. Values in parentheses are based on the amount of complex which reacted where reaction was not complete. [b] In two early experiments, cyclooct-4-enone was not observed, but 1,5-cyclooctadienyl ether was (retention time, 67 min). In later experiments, only the cyclooctenone could be found. [c] In this experiment, the 2,4-dinitrophenylhydrazone of formaldehyde was obtained in 51% yield.

cyclooctadiene)palladium(II) (1) and its methoxy adduct, 2, are refluxed in methanol will be described.



1 2 (X = Cl, OMe)

The cyclooctadiene palladium chloride complex, 1, is prepared by precipitating it from a solution of sodium tetrachloropalladate(II) and 1,5-cyclooctadiene in methanol. The methoxy–palladium chloride adduct, 2-Cl, can be formed by stirring the diene complex in methanol with sodium carbonate. Reaction with 1 equiv of sodium methoxide might seem a reasonable alternate method,[5] but with this system we found that a di-μ-methoxido–methoxy adduct was formed, di-μ-methoxidobis(2-methoxycyclooct-5-enyl)dipalladium(II) (2-OMe).

Dichloro(1,5-cyclooctadiene)palladium(II) (1), which is only slightly soluble in methanol does not react when a suspension is stirred and refluxed (68 °C) for 10 h. Less than 0.1% decomposed. When this diene complex is refluxed in methanol with various added bases, palladium metal is precipitated quantitatively as a mirror and small particles within 1–3 h.

When the adduct 2-Cl is refluxed in methanol without added base, hydrogen chloride is formed as the reaction proceeds in addition to palladium metal and organic products. This hydrogen chloride reacts with the unreacted adduct 2-Cl converting it to diene complex 1 which is stable in refluxing methanol in the presence of hydrogen chloride. As can be seen in Table I, after 5 h, a 53% yield of palladium was found and a 45% yield of 1 was recovered. In the presence of sodium carbonate 2-Cl gives no 1 (Table I), but like the methoxido adduct 2-OMe gives palladium and oxidized products. In the rest of the experiments in Table I, 1 was stirred with base in methanol until the yellow color of 1 disappeared and then was refluxed for the times stated.

The organic product mixtures were analyzed by gas chromatography. The percentage yields of products from these reactions are listed in Table I. The organic products were identified by comparison of the gas chromatograph retention time and the NMR, ir, and uv spectra of collected peaks with those of samples synthesized in independent ways. The organic products from the methanolysis reactions were 1,5-cyclooctadiene, cyclooctyl methyl ether, 4-cyclooctenyl methyl ether, 2,4-cyclooctadienyl methyl ether, 2,5-cyclooctadienyl methyl ether, 3,5-cyclooctadienyl methyl ether, cyclooctanone, 4-cyclooctenone, and palladium metal. All of these products, except 1,5-cyclooctadienyl methyl ether, which is discussed later, were found to be stable in methanol in the presence of hydrogen chloride, sodium carbonate, sodium methoxide, and 1 for the reaction times. The syntheses of these compounds will be found in the Experimental Section. The organic product yields were calculated by adding a calibrated internal standard. Total palladium metal was measured by filtering the reaction solution and weighing.

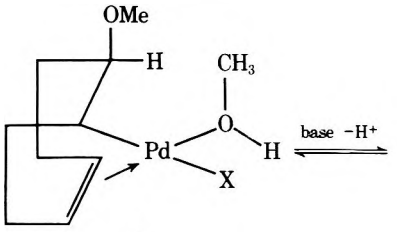
The methanolysis products arise from two primary reactions of the methoxypalladium adduct: (1) the reductive cleavage of the carbon–palladium σ bond by complexed alcohol yielding a monoenyl ether and (2) the β-elimination of HPdX yielding a dienyl ether. The very minor amount of saturated compounds probably arise from the hydrogenation of the double bond by palladium hydride formed in situ. Formation of 1,5-cyclooctadiene may be explained by the deoxypalladation of the adduct which is minor in the solvolysis of the methoxy adduct.

The reductive cleavage product is 4-cyclooctenyl methyl ether. Tsuji[6] noted that degradation of the methoxy adduct, 2-Cl, with methoxide yielded 4-cyclooctenyl methyl ether and that a similar reductive cleavage of di-μ-chlorobis(8-diethoxycarbonylmethyl-4-cyclooctenyl)dipalladium(II) by ethoxide in ethanol yielded 4-cyclooctenyl malonate. The ethanol was presumed to be oxidized to acetaldehyde which was not

isolated. Base and ethanol has been used as a reducing agent for producing hydridoplatinum complexes.[7]

When the diene complex, **1**, was solvolyzed in methanol with excess sodium carbonate, the 4-cyclooctenyl methyl ether isolated (36.8% yield, see Table I) by gas chromatography showed a parent peak in the mass spectrum at *m/e* 140. The methyl ether from the solvolysis in methanol-d_1 was collected and the mass spectrum showed the parent peak at *m/e* 140 which is the same as in the undeuterated methanol from above. The P:P + 1 ratio was within experimental error of the value calculated on the basis of the natural abundance of isotopes. The same reaction of the diene complex, **1**, in methanol-d_4 gave 4-cyclooctenyl methyl ether with the parent peak at *m/e* 144 demonstrating that this product contained four deuterium atoms. Three of the deuterium atoms must be on the methyl group as the methoxy adduct **2**-Cl was prepared in situ, and one was introduced at C-2 from the methanol-d_4 methyl group in the reductive cleavage reaction.

In another experiment, when the reaction product solution (after filtering off the palladium metal) was treated with 2,4-dinitrophenylhydrazine reagent, a yellow solid was formed. This turned out to be the 2,4-dinitrophenylhydrazone of formaldehyde by melting point and mixture melting point, and the yield of this 2,4-dinitrophenylhydrazone corresponded to the yield of 4-cyclooctenyl methyl ether. A mechanism for this reductive cleavage of the carbon–palladium σ bond by complexed alcohol can be formulated as shown, **3** → **4** → **5**.



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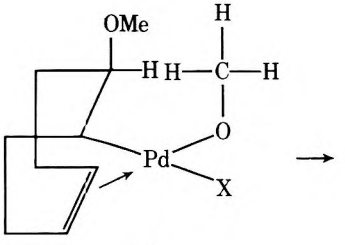

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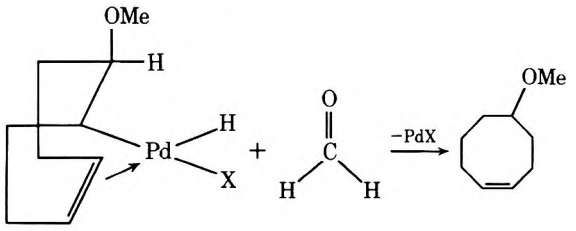

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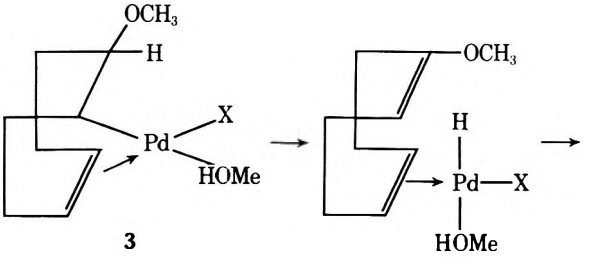
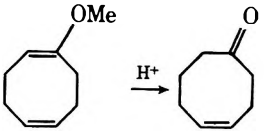
The reacting species in methanol is not the binuclear adduct di-μ-chlorobis(2-methoxycyclooct-5-enyl)dipalladium (**2**-Cl), because it is largely solvolyzed in methanol solution yielding a methanol coordinated palladium species, **3**.[8] Base removes a proton giving a methoxidopalladium intermediate, **4**. That this methoxidopalladium intermediate is the reactive species is suggested by the increasing yield of 4-cyclooctenyl methyl ether with increasing base strength. Compare data in Table I for reactions with no base (and hence in the presence of developing HCl) with those with added sodium carbonate and with added sodium methoxide. With no base present, the yield of 4-cyclooctenyl methyl ether is only 3%, but in the presence of base the yield increases to 37–60%. However, in sodium methoxide, the complex must be almost all the methoxidopalladium species **4** because increasing the sodium methoxide concentration makes only a small increase in the monoenyl ether.

The β-elimination of HPdX from **2** yields dienyl ethers (Table I). The 4-cyclooctenone obtained is formed from a β-elimination of the adduct yielding 1,5-cyclooctadienyl methyl ether (**7**) which in the presence of acid or palladium(II) converts to the 4-cyclooctenone. In early experiments with base present the vinyl ether **7** was observed instead of the ketone, but in later runs only the unsaturated ketone was found. The vinyl ether was identified by the ir and NMR spectra of the collected GC peak as well as by the observation that addition of aqueous acid converted it to 4-cyclooctenone. We were unsuccessful in preparing this compound by another route, no doubt because of the large strain energy of the cyclooctadiene system.[9] The reason that it could not be isolated in later experiments could be isomerization in the gas chromatograph despite efforts to prevent it. Thus, the total percentage of products to or through dienyl ethers (including 4-cyclooctenone) ranges from 71.3% of the oxidized organic product in acidic solution to 38% in basic solution (see Table I).

As pictured **3** → **6**, a cis β-elimination of HPd from the trans adduct leads to a 1,5-cyclooctadienyl ether **7** which in acidic



3 **6**



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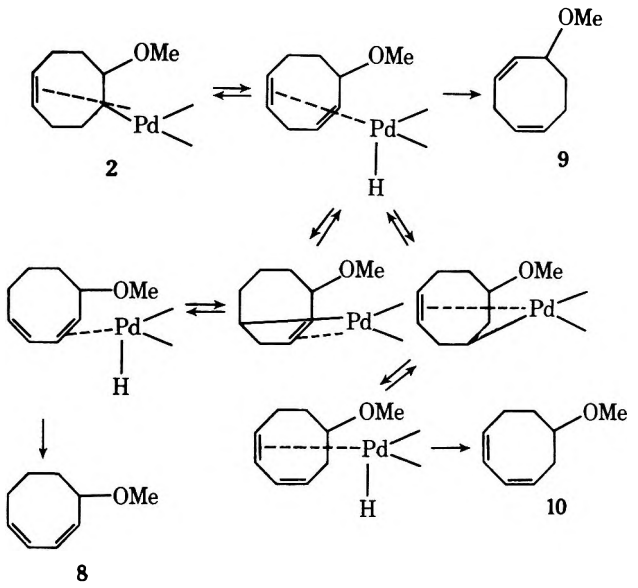
solution would form 4-cyclooctenone. A trans β-elimination of the elements of HPdX could only result from a cis adduct, but also should be base catalyzed, since the base would be able to assist in pulling off the hydrogen trans to the palladium to give the dienyl product. However, the data do not support this because much more 4-cyclooctenone is formed in acidic solution with no added base (see Table I). The isomerization by β-elimination–addition (see below) will not lead to vinyl ether unless the adduct was originally trans (or unless the olefin moiety is free from the palladium at some stage). Thus, vinyl ether and hence 4-cyclooctenone arise via cis β-elimination of HPdX from a trans adduct.

A cis β-elimination of HPd from **2** would also be expected to form the 2,5-cyclooctadienyl methyl ether. Although the 2,5-dienyl ether is stable in refluxing methanol in the presence of acid or bases or **1** for these reaction times, other dienyl ethers are found besides. Consequently it is proposed that intermediate olefin hydridopalladium species readd and undergo elimination leading to the other dienyl ethers as shown below (**2** → **8**, **9**, **10**). Such elimination–addition has been proposed before for olefin isomerization by Pd^{II}.[10]

Although the rearrangement of dienyl ethers is easily rationalized, the reason for the relative amounts of each isomer is not obvious. In the literature the 3,5-cyclooctadienyl derivatives appear to be more stable than the 2,4- inasmuch as



2,4- will thermally isomerize to 3,5-.[11] Probably the differences in the product yields can be attributed to the different reactivities of the various reactive intermediates which would be present under the different reaction conditions (3-Cl, 3-OCH_3, and 4-Cl) and of the hydrido intermediates 5-Cl, 6-Cl, and 6-OMe.

Another anomaly is that the product composition of the reactions in the presence of sodium carbonate does not change when they are refluxed longer than needed to give a quantitative yield of palladium. This is not the case for the reactions with added sodium methoxide. Even though the yield of palladium is within experimental error of quantiative, the ether product distribution changed under continued reflux.

As pointed out earlier, if there is insufficient sodium carbonate to neutralize product hydrogen chloride, 1 will be formed. The hydrogen chloride arises as follows:

$$(COD)PdCl_2 + 2MeOH \rightarrow (CODOMe)PdCl(MeOH) + HCl$$

$$(CODOMe)PdCl(MeOH) \rightarrow \text{products} + Pd + HCl$$

In Table I where one might think 3.05 mmol of sodium carbonate should neutralize 2.44 mmol of 1, it can be seen that 1 mol of sodium carbonate only neutralizes 1 mol of hydrogen chloride. Apparently sodium bicarbonate does not neutralize the hydrogen chloride so that it cannot react with the intermediates to form 1. Furthermore, in Table I where the ratio of 1 to sodium methoxide is 1:1, the reaction goes quantitatively to palladium(0) and oxidized organic products instead of yielding a 50% yield of 1 back again. The only conclusion we can draw is that hydridopalladium species do not decompose to metal immediately, but are relatively long lived, more so in the sodium methoxide reactions than in those with carbonate. Perhaps related is the ease of reduction of carbonate phosphine platinum complexes.[12]

A final anomaly is the observation that although some cyclooctadiene is formed in some reactions, nevertheless the yield of palladium is essentially quantitative. Note that deoxymetalation of 2 would lead to cyclooctadiene and palladium(II) (no oxidation–reduction). The facts can, however, be explained as the result of deoxymetalation of a species like 5, the hydridopalladium adduct, which would deoxypalladate to cyclooctadiene and palladium and hydrogen chloride ultimately.

Experimental Section

Chloro Complexes. Dichloro(1,5-cyclooctadiene)palladium(II) (1) was prepared by Chatt's method: mp 210 °C dec (lit.[2] 205–210 °C dec); NMR spectral resonances at 6.48 (multiplet, 4 protons) and 2.80 ppm (m, 8 protons); uv spectrum λ_{max} 347.5 nm (ϵ 1680) in chloroform. Di-μ-chlorobis(2-methoxycyclooct-5-enyl)dipalladium(II) (2-Cl): mp 150–155 °C dec (lit.[2] 136–140 °C dec); NMR (chloroform) 1.60 (m, 1), 2.00 (m, 4), 2.40 (m, 4), 3.21 (s, 3), 3.60 (m, 1), 5.70 ppm (m, 2); uv spectrum λ_{max} 325 nm (ϵ 3430) in chloroform.

Di-μ-methoxido(2-methoxycyclooct-5-enyl)dipalladium(II) (2-OMe). To a solution of 1.50 g (0.0268 mol) of sodium methoxide in 50 ml of methanol cooled to −20 °C was added 3.00 g (0.011 mol) of 1. After a few minutes, a white solid formed which was filtered, washed with methanol, and dried to yield 2.60 g (90%) of 2-OMe, mp 110–120 °C dec.

Anal. Calcd for $C_{20}H_{36}O_4Pd_2$: C, 43.42; H, 6.56; Pd, 38.46. Found: C, 43.17; H, 6.74; Pd, 38.22. NMR spectrum (chloroform) 1.5 (m, 1), 2.00 (m, 4), 2.60 (m, 4), 3.22 (s, 3), 3.28 (s, 3), 3.60 (m, 1), 5.20 ppm (m, 2); uv (chloroform) λ_{max} 315.0 nm (ϵ 3510).

Solvolysis Method. A weighed sample of the complex was added to a solution of sodium methoxide or a slurry of sodium carbonate in 15 ml of methanol. The mixtures were stirred at room temperature until the yellow color of the diene complex disappeared, and then the mixtures were heated at reflux for the times given in Table I. After cooling, the palladium black was filtered off on a sintered glass funnel, washed with methanol and water, and dried to constant weight. The organic products in Table I were analyzed by GC using a 3 m × 0.25 in. column of 20% Carbowax 4000 on non-acid-washed 60/80 mesh Chromosorb W operated at 100 °C and 13 psi. Under these conditions the retention times are as follows: 1,5-cyclooctadiene, 15 min; cyclooctyl methyl ether, 36 min; 4-cyclooctenyl methyl ether, 39 min; 2,4-cyclooctadienyl methyl ether, 40.5 min; 2,5-cyclooctadienyl methyl ether, 50.5 min; 3,5-cyclooctadienyl methyl ether, 52 min; cyclooctanone, 94 min; 4-cyclooctenone, 106 min. Percentages of products were obtained by using a calibrated internal standard, 1,5-cyclooctadiene. The GC peaks were cut out and weighed. Thermal response differences were taken into account in calculating yields.

In two early experiments, cyclooct-4-enone was not observed among the products of methanolysis in the presence of sodium carbonate (Table I). Instead, a peak was observed at a retention time of 67 min. Treatment of the product mixture with a drop of dilute sulfuric acid caused the 67-min peak to disappear and the appearance of the 4-cyclooctenone peak at 106 min. The 67-min peak is thought to be the 1-methoxy-1,5-cyclooctadiene. A weak, possibly impure NMR spectrum of the collected peak showed resonances at δ 5.9, 5.1, 3.7, and 2.4 ppm. The ir spectrum of the collected peak showed absorptions at 1702 (s), 1670 (m), besides 3010 (m), 2940 (vs), 2850 (s), 1475 (s), 1100 cm^{-1} (vs).

In experiments where the yield of formaldehyde was measured (Table I), the reaction solution after GC analysis was added to 2,4-dinitrophenylhydrazine solution prepared according to the instructions of Shriner, Fuson, and Curtin.[13] The solid 2,4-dinitrophenylhydrazone was chromatographed and recrystallized, 0.34 g (51%), mp 166–168 °C (lit.[13] mp 166 °C). A mixture melting point with an authentic sample was not depressed.

4-Cyclooctenyl Methyl Ether. 4-Cyclooctenol[14] (2 g, 0.016 mol) was added to sodium hydride (1 g, 0.22 mol) 54% in mineral oil suspended in dimethylformamide and stirred for 1 h. Methyl iodide (3 g, 0.021 mol) was added slowly, and the mixture was stirred for 1 h. Water was added dropwise with stirring. The mixture was extracted with ether. After drying and concentrating the ether solution, the product was distilled 1.7 g (76%), bp 45–47 °C (4 mm).

Anal. Calcd for $C_9H_{16}O$: C, 77.67; H, 11.50. Found: C, 77.67; H, 11.75. NMR spectrum δ 1.5–1.9 (m, 6), 1.9–2.4 centered at 2.1 (m, 4), 3.18 (s, 3), 3.2 (m, 1), 5.5 ppm (broad m, 2).

Cyclooctyl Methyl Ether. The saturated ether was prepared from commercially available cyclooctanol by the method as described above: bp 58–60 °C (5 mm) [lit.[15] bp 76–77 °C (18 mm)]; NMR spectrum δ 1.55 (m, 14), 3.12 (s, 3), 3.10 ppm (m, 1).

4-Cyclooctenone. A 10% solution of 4 g (0.032 mol) of 4-cyclooctenol[14] in pyridine was added to 4.5 g (0.045 mol) of chromium trioxide in 45 ml of pyridine and stirred for 24 h. Water was added, and the mixture was extracted with ether. The ether solution was washed with water and 10% hydrochloric acid, dried over K_2CO_3, and concentrated. Distillation gave 2 g (50%) of the ketone: bp 50–53 °C (2 mm); NMR spectrum δ 1.4 (broad m, 10), 2.2 ppm (m, 4); ir spectrum 3020 (m) 2940 (s), 2850 (m), 1710 (vs), 1475 (m), 1340 (m), 740 cm^{-1} (m). 2,4-Dinitrophenylhydrazone was made and purified by column chromatography, mp 187–189 °C (lit.[16] 194–196 °C).

2,4-Cyclooctadienyl Methyl Ether. 2,4-Cyclooctadienyl acetate was prepared by Cope's method,[17] bp 50–55 °C (0.3 mm) [lit.[17] 56–57 °C (0.6 mm)]. To a solution of 2 g (0.012 mol) of 2,4-cyclooctadienyl acetate dissolved in dry dimethylformamide was added 1.5 g (0.033

mol) of sodium hydride 54% in mineral oil. After stirring for 1 h, methyl iodide (9 g, 0.064 mol) was added slowly, and stirring was continued for 1 h. Water was added dropwise, and the mixture was extracted with ether. The ether solution was washed with water and dried over K_2CO_3. After evaporation of ether, the residue was distilled, bp 40–43 °C (2 mm), 0.7 g (42%).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.40; H, 10.31. NMR spectrum δ 1.1–1.9 (m, 4), 1.9–2.2 (m, 2), 3.21 (s, 3), 3.90 (m, 1), 5.3–6.0 ppm (m, 4).

2,5- and 2,6-Cyclooctadienyl Acetate. Method A. A suspension of 70 g (0.22 mol) of mercuric acetate, 30 g (0.28 mol) of 1,5-cyclooctadiene, and 50 ml of acetic acid was refluxed for 3 h, producing metallic mercury. The brown solution was decanted from the mercury, and 300 ml of ether added. The ether solution was extracted with water and saturated sodium bicarbonate solution, dried, and concentrated. The residue was distilled, bp 75–77 °C (2 mm), giving 21 g (58%) of a mixture of 7% 2,5- and 93% 2,6-cyclooctadienyl acetate by GC peak areas. The peaks were separated by GC.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found for the 2,5 isomer: C, 72.17; H, 8.66. For the 2,6-isomer: C, 72.43; H, 8.75.

Method B. A mixture of 30 g (0.28 mol) of 1,5-cyclooctadiene and 40 g (0.22 mol) of *N*-bromosuccinimide in 200 ml of carbon tetrachloride was refluxed with a catalytic amount of 2,2′-azobis-2-methylpropionitrile for about 5 h. The succinimide was filtered off, and the solution was washed with hot water and saturated sodium carbonate solution and dried over sodium carbonate. After the solvent was removed under reduced pressure, the residue was dissolved in 50 ml of acetic acid. Silver acetate (37 g, 0.22 mol) suspended in 200 ml of acetic acid was added slowly with cooling and stirring. The silver bromide was filtered off and 300 ml of ether was added to the solution which was then washed with water and aqueous sodium bicarbonate and dried. After the solvent was removed, the residue was distilled, bp 62–68 °C (1 mm), giving 24 g (65%) of a mixture of 30% 2,5- and 70% 2,6-cyclooctadienyl acetates.

2,5- and 2,6-Cyclooctadienol. A mixture of 20.0 g (0.12 mol) of 93% 2,6- and 7% 2,5-cyclooctadienyl acetate was added to 15 g of sodium hydroxide dissolved in 200 ml of methanol and refluxed for 1 h. The mixture was neutralized with dilute hydrochloric acid and extracted with ether. After drying and removal of the ether, the residue was distilled, giving 13.6 g (91%), bp 70–78 °C (1 mm), of a mixture of 89% 2,6- and 11% 2,5-cyclooctadienols as determined by GC. The isomers were separated by GC.

Anal. Calcd for $C_8H_{12}O$: C, 77.36; H, 9.74. Found for 2,6 isomer: C, 77.21; H, 9.86. For the 2,5 isomer: C, 77.59; H, 9.89.

2,5- and 2,6-Cyclooctadienyl Methyl Ethers. A mixture of 2,5- and 2,6-cyclooctadienol (10.0 g, 0.08 mol) was added slowly to 200 ml of ether containing 10 g (0.17 mol) of a 40% sodium dispersion (5 μ) in xylene. The mixture was stirred for 1 h, whereupon 20 g (0.14 mol) of methyl iodide was added. After the mixture was stirred for 12 h and refluxed for 2 h, methyl alcohol was added dropwise consuming the excess sodium. More ether was added, and the solution was washed with water and dried. After the ether was removed, the residue was distilled giving 7.9 g (72%), bp 42–45 °C (2 mm), of a mixture of 86% 2,6- and 14% 2,5-cyclooctadienyl methyl ether by GC. The isomers were separated by GC.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found for the 2,5 isomer: C, 77.96; H, 10.07. For the 2,6 isomer: C, 78.07; H, 10.13. NMR spectrum for 2,5 δ 1.00–1.70 (m, 2), 1.70–2.10 (m, 2), 2.70–2.90 (m, 2), 3.21 (s, 3), 4.00–4.50 (m, 1), 5.05–5.80 ppm (m, 4); for 2,6 δ 1.80–2.80 (m, 6), 3.21 (s, 3), 4.50 (m, 1), 5.40 ppm (m, 4).

3,5-Cyclooctadienyl Acetate. Employing the method of Crandall,[11] 10 g (0.093 mol) of 1,3-cyclooctadiene and 10 g (0.09 mol) of selenium dioxide in 60 ml of acetic acid were refluxed for 13 h. After 150 ml of water was added, the solution was neutralized with sodium carbonate and steam distilled. The distillate was extracted with ether. After the ether solution was dried, the ether was removed and the residue was distilled, giving 4.8 g (31%) of the 3,5-acetate, bp 63–65 °C (2 mm). If this reaction was terminated after 4 h, the product was 2,4-cyclooctadienyl acetate, 5.2 g (33%), bp 69–72 °C (3 mm) [lit.[17] 56–57 °C (0.6 mm)]. Mercuric acetate oxidation of 1,3-cyclooctadiene gave similar results. The 3,5-acetate was also obtained by brominating cyclooct-4-enyl acetate with *N*-bromosuccinimide (as described above) and eliminating the elements of hydrogen bromide by treating the bromocyclooct-4-enyl acetate with magnesium hydrogen orthophosphate trihydrate in dimethylformamide at 80 °C for 36 h. NMR spectrum for 3,5 isomer δ 1.70 (m, 2), 2.30 (m, 4), 1.98 (s, 3), 4.75 (m, 1), 5.70 ppm (m, 4).

3,5-Cyclooctadienyl Methyl Ether. Cycloocta-3,5-dienyl acetate (2 g, 0.012 mol) in 10 ml of ether was added dropwise to 1 g (0.026 mol) of lithium aluminum hydride in 25 ml of ether, and the mixture was stirred for 30 min. Water was added dropwise until the excess hydride had reacted. After 10 ml of saturated ammonium chloride solution was added, the ether solution was separated, washed with water, and dried. After the ether was removed, the alcohol was etherified in procedure similar to that above for the cyclooct-4-enyl methyl ether. The ether product distilled, bp 40–42 °C (1 mm), giving 1.2 g (72%).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.23; H, 10.34. NMR spectrum δ 1.44–2.20 (m, 2), 2.20–2.50 (m, 4), 3.22 (s, 3), 3.20–3.40 (m, 1), 5.40–5.80 ppm (m, 4).

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Registry No.—**1**, 12107-56-1; **2**-Cl, 12096-15-0; **2**-OMe, 58384-26-2; **7**, 58343-31-0; **8**, 58343-32-1; **9**, 58343-33-2; **10**, 58343-34-3; 4-cyclooctenyl methyl ether, 13366-81-9; 4-cyclooctenol, 4277-34-3; methyl iodide, 74-88-4; cyclooctyl methyl ether, 3637-63-6; cyclooctanol, 696-71-9; 4-cyclooctenone, 6925-14-0; 2,4-cyclooctadienyl acetate, 10095-82-6; 2,5-cyclooctadienyl acetate, 23346-41-0; 2,6-cyclooctadienyl acetate, 23346-42-1; 1,5-cyclooctadiene, 111-78-4; 2,5-cyclooctadienol, 10054-74-7; 2,6-cyclooctadienol, 10017-18-2; 2,6-cyclooctadienyl methyl ether, 16538-86-6; 3,5-cyclooctadienyl acetate, 10095-81-5.

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Additions and Cycloadditions of Cyclopentadienyl Metal Compounds to Benzyne

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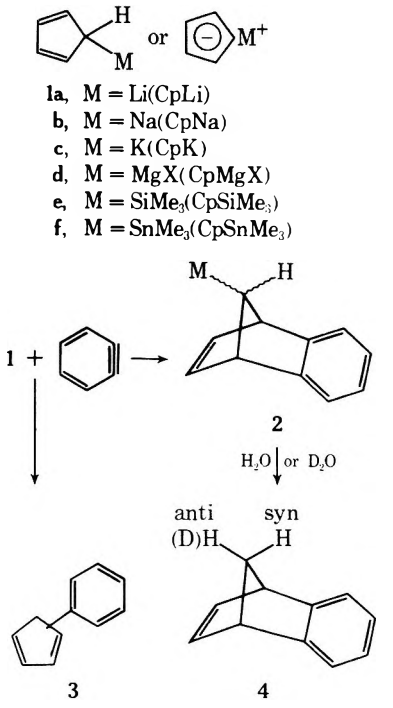
Cyclopentadienyllithium, -sodium, and -potassium add to benzyne, generated from metal amides and chlorobenzene in tetrahydrofuran (THF), to form phenylcyclopentadiene (**3**) in low yields. In contrast, cyclopentadienylmagnesium halides (CpMgX), trimethylsilylcyclopentadiene, and trimethylstannylcyclopentadiene ($CpSnMe_3$) cycloadd to benzyne, generated from *o*-bromofluorobenzene and magnesium in THF, to give 7-benzonorbornadienyl metal compounds (**2**). The major product from $CpSnMe_3$, however, is *o*-fluorotrimethylstannylbenzene. In the presence of 2 equiv of hexamethylphosphoramide, CpMgBr and benzyne produce both **2** and **3**. The results suggest a σ-bonded structure for the CpMgX which cycloadds to benzyne.

Benzyne is a highly reactive dienophile in [2 + 4] cycloadditions, undergoes [2 + 2] cycloadditions, is very susceptible to nucleophilic additions, participates in the ene reaction, and inserts into carbon–hydrogen bonds.[2] It cycloadds to both cyclopentadiene and cyclopentadienylmagnesium bromide (**1d**, CpMgBr) in refluxing tetrahydrofuran (THF) to give benzonorbornadiene (**4**) in 66 and 21% yields, respectively.[3] Deuterolysis after the CpMgBr reaction leads to **4** with 0.91 atom excess deuterium located exclusively in the anti-7 position, implying that cycloaddition produces 7-benzonorbornadienylmagnesium bromide (**2**, M = MgBr).[4] Benzyne also cycloadds to methyl-, 1,3-dimethyl-, trimethylsilyl-, and *tert*-butylcyclopentadienes and to the corresponding cyclopentadienylmagnesium chlorides to give substituted benzonorbornadienes.[5]

To determine whether the structure of CpMgBr which cycloadds to benzyne is σ- (monohapto) or π- (pentahapto) bonded, we have studied reactions of benzyne with a variety of other metallocyclopentadienes (**1**). If σ-bonded CpMgBr is the reactive species, the cycloaddition is a common Diels–Alder reaction of a 5-metallocyclopentadiene, whereas if π-bonded CpMgBr is the reactive species, the reaction is a highly unusual cycloaddition of a delocalized cyclopentadienyl anion to benzyne.



1a, M = Li(CpLi)
b, M = Na(CpNa)
c, M = K(CpK)
d, M = MgX(CpMgX)
e, M = $SiMe_3$($CpSiMe_3$)
f, M = $SnMe_3$($CpSnMe_3$)

Results

Benzyne was generated from *o*-bromofluorobenzene and magnesium turnings in THF for reactions of cyclopentadienylmagnesium, silicon, and tin compounds, and from chlorobenzene and either lithium 2,2,6,6-tetramethylpiperidide, sodium amide, or potassium amide for reactions of cyclopentadienylalkali compounds. Although many other methods of benzyne generation are known,[2] the methods chosen appeared to be the most compatible with metallocyclopentadienes.

The products from these metallocyclopentadienes and benzyne are shown in Table I. Treatment of ferrocene with benzyne generated by the organomagnesium route gave no detectable phenylcyclopentadiene (**3**) or benzonorbornadiene (**4**) and left much unreacted ferrocene. We usually tried to identify only **2**–**4**. The low yields are probably due to (a) other reactions of benzyne, such as formation of biphenylene and triphenylene,[6] (b) reactions of benzyne with the adducts, and (c) instability of phenylcyclopentadiene (**3**). The 1,4-diphenylcyclopentadiene and pentaphenylcyclopentadiene isolated from the CpNa reactions are examples of further reactions of 1:1 adducts with benzyne. Upon standing overnight after GLC isolation, **3** dimerized or polymerized. Since the efficiencies of its polymerization while standing in THF prior to GLC isolation, and its depolymerization in the injection port of the gas chromatograph, are not known, yields of **3** are only lower limits. On the other hand, products **2** and **4** listed in Table I were quite stable to the isolation conditions and could be detected if present in yields of ≥0.05% by GLC–mass spectrometry. The varied methods of benzyne generation must also affect the yields.

Reaction of $CpSnMe_3$ and benzyne produced benzonorbornadiene (**4**), o-fluorotrimethylstannylbenzene (**5**), and *anti*-7-trimethylstannylbenzonorbornadiene (**2**, M = *anti*-$SnMe_3$). Although **4** and **5** could not be separated by preparative GLC, they were identified by GLC–mass spectrometry, elemental analysis, and ^1H NMR as an 8.3:91.7 mixture. Displacement of cyclopentadienide from $CpSnMe_3$ by *o*-fluorophenylmagnesium bromide, the intermediate which leads to benzyne,[2] is analogous to the transmetalations of allyl- and vinylstannanes with lithium alkyls which produce allyl- and vinyllithium.[7] Reaction of benzyne with the displaced CpMgBr may account for the small amount of **4** produced. The configuration of **2** (M = *anti*-$SnMe_3$) was established by ^1H NMR experiments which detected long-range coupling between the syn-7 proton and vinyl protons.[8–10]

Discussion

Most of the reactivity differences in Table I may be attributed to a fundamental structural difference between al-

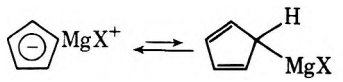
Table I. Reactions of Metallocyclopentadienes and Benzyne

Reactant	% yield[a] 2	4	3[b]
CpLi		0	3.9
CpNa[c]		0	9.9[d]
CpK		0	0.9
CpMgBr[e]		21–29	0
CpMgCl–HMPA		0.24	1.1
$CpSiMe_3$[f]	52		0
$CpSnMe_3$[g]	1.9	3.6	0

[a] Determined by GLC and based on equimolar amounts of CpM and the benzyne precursor. Of products 2 only the M = $SiMe_3$ and M = $SnMe_3$ compounds withstand hydrolysis. [b] Yields of 3 are lower limits because of its instability (see text). [c] Also isolated were 1,4-diphenylcyclopentadiene (2.1%) and pentaphenylcyclopentadiene (1.7%). [d] A tenfold excess of CpNa gave 3 in 80% yield (ref 26). [e] References 3 and 4. [f] Reference 5. [g] Also isolated was o-fluorotrimethylstannylbenzene (32.1%).

kali cyclopentadienides on the one hand and $CpSiMe_3$ and $CpSnMe_3$ on the other. Solid-phase ir spectra of CpLi, CpNa, and CpK[11a,b] and ir and uv spectra of CpLi and CpNa in THF solutions[11c] support pentahapto structures in which the metal is located near the C_5 axis of the cyclopentadienide. As 1 M THF solutions employed here, the alkali cyclopentadienides should consist of ion aggregates. $CpSiMe_3$ at room temperature is a mixture of 3% 1-, 7% 2-, and 90% 5-substituted[12] σ-bonded isomers,[13–15] which cycloadd to benzyne in 52% yield to produce 16% 1-, 12% 2-, 2% *syn*-7-, and 70% *anti*-7-trimethylsilylbenzonorbornadienes.[5] $CpSnMe_3$ has been shown by electron diffraction,[16] ir,[14] NMR,[17] and mass spectroscopic[13] methods to be σ bonded also. Excluding cyclopentadienylmagnesium compounds the reactivity pattern is clear: ionic pentahapto metallocyclopentadienes undergo nucleophilic addition to benzyne to produce phenylcyclopentadiene, while covalent monohapto metallocyclopentadienes cycloadd to produce metallobenzonorbornadienes. Ferrocene has a pentahapto structure[18] but is too weakly nucleophilic to add to benzyne under our conditions.

What is the structure of the cyclopentadienylmagnesium halide which cycloadds to benzyne? Gas-phase electron diffraction[19] and solid-phase x-ray diffraction[20] studies indicate D_{5h} or D_{5d} symmetry for dicyclopentadienylmagnesium (Cp_2Mg), and an x-ray crystal structure of the tetraethylethylenediamine solvate of CpMgBr shows that the metal atom lies near the cyclopentadienide C_5 axis.[21] Although solid- and gas-phase structures are not necessarily the same as structures in solution, ir and uv spectra of Cp_2Mg, CpMgCl, and CpMgBr in THF also support pentahapto structures.[11c] It is possible that as much as 5–10% of a monohapto CpMgX could exist in equilibrium with the pentahapto species in THF solution (eq 1) and not be de-



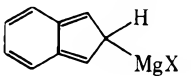
(1)

tected by ir or uv. From the reactivity pattern observed for the other metallocyclopentadienes, we propose that the CpMgX which cycloadds to benzyne is σ bonded.

In the presence of 2 equiv of hexamethylphosphoramide (HMPA) CpMgCl and benzyne produced traces of both 3 and 4, and after deuterolysis the benzonorbornadiene contained excess deuterium according to its mass spectrum. The high affinity of HMPA for magnesium is known to increase greatly the ionic character of organomagnesium compounds.[22] HMPA could shift the equilibrium of eq 1 far to the left, which would inhibit cycloaddition of the σ-bonded form and give CpMgCl properties similar to those of alkali cyclopentadienides.

The stereospecificity of benzyne addition to $CpMgX$[4,5] can be explained readily by reaction of the σ-bonded isomer. Methyl, trimethylsilyl, and trimethylstannyl groups at the 5 position of cyclopentadiene all produce predominantly anti-7-substituted benzonorbornadienes, presumably because of steric hindrance between the substituents and benzyne in the transition states leading to the corresponding syn isomers. A magnesium halide group with its THF solvation shell is certainly more bulky than a methyl group and may be even larger than trimethylsilyl and trimethylstannyl groups. Therefore benzyne prefers to cycloadd to the side of the cyclopentadiene opposite the magnesium to form *anti*-7-benzonorbornadienylmagnesium halide. Deuterolysis with retention of configuration then produces exclusively benzonorbornadiene-*anti*-7-*d*.

Indenylmagnesium bromide in THF also cycloadds to benzyne to produce 9,10-dihydro-9,10-methanoanthracene.[4,23] Isoindenylmagnesium halide (6) is required to ex-



6

plain this result with a σ-bonded intermediate. In metalloindenes the rates of [1,2] metallotropic shifts are known to increase in the order H < Si < Ge < Sn.[24] Although the highly endothermic conversion of indene to isoindene by a [1,5] sigmatropic hydrogen shift proceeds readily only at >200 °C,[25] the conversion of indenylmagnesium halide to 6 might occur readily by a [1,2] metallotropic shift. Indeed, the trimethylsilyl analogue of 6 has been trapped in a Diels–Alder reaction with tetracyanoethylene at room temperature.[24a] Also in agreement with our proposal of cycloaddition of benzyne to a σ-bonded metalloindene is the failure of indenyllithium and indenylsodium to form cycloadducts with benzyne.[26]

Experimental Section

General. Microanalyses were performed by J. Nemeth and associates. Infrared spectra were obtained either as a thin film between sodium chloride plates with a Perkin-Elmer Model 237B instrument or as a potassium bromide pellet with a Beckman IR-12 instrument. ^1H NMR spectra were obtained on Varian T-60, A-60A, A-56/60, or HA-100 spectrometers with Me_4Si as an internal standard except with compounds containing tin. The HA-100 equipped with a Hewlett-Packard Model 200ABR audio oscillator was used for decoupling experiments. Routine mass spectra were recorded on a Varian-MAT CH-5 mass spectrometer. GLC–mass spectrometry experiments were performed with a 6-ft 3% SE-30 on 100/120 Gas Chrom Q glass column on a Varian-MAT CH-7 mass spectrometer equipped with a Varian Model 2700 gas chromatograph. GLC analyses were performed on a 0.125 in. × 4 ft 20% Apiezon L on 60/80 Chromosorb W column with a helium flow of 20 ml/min on a Hewlett-Packard Model 700 instrument equipped with a thermal conductivity detector. Product yields were determined relative to an *n*-alkane internal standard without correction for thermal conductivity differences. Preparative GLC separations were performed on a Varian Model A-90-P instrument using a 0.25 in. × 10 ft 10% SE-30 on 60/80 Chromosorb W column with a helium flow of 60 ml/min. All reactions were performed with dry glassware under a dry nitrogen atmosphere.

Materials. The *o*-bromofluorobenzene (Aldrich), chlorotrimethylstannane (Aldrich), magnesium turnings (Baker), sodium amide (Fisher), *n*-BuLi in hexane (titrated as 2.31 M, Alfa), and 3.1 M ethylmagnesium chloride in ether (Alfa) were used as obtained. The chlorobenzene (Fisher), 2,2,6,6-tetramethylpiperidine (Aldrich), and hexamethylphosphoramide (Aldrich) were distilled from calcium hydride under nitrogen. Cyclopentadiene was prepared by cracking its dimer immediately before use. Tetrahydrofu-

ran was distilled under nitrogen from sodium benzophenone ketyl just before use.

Cyclopentadienyllithium (1a) and Benzyne. A solution of 3.3 g (50 mmol) of cyclopentadiene and 7.77 g (55 mmol) of 2,2,6,6-tetramethylpiperidine in 30 ml of THF was added dropwise over a period of 30 min to 104 mmol of *n*-butyllithium in hexane at −78 °C. A white precipitate formed during the addition. After the mixture had warmed to room temperature, the solvent was removed under vacuum and replaced with 30 ml of THF. The white solid dissolved. The solution was heated to reflux, and 5.63 g (50.0 mmol) of chlorobenzene in 20 ml of THF was added dropwise over a period of 40 min. Reflux was continued for 1 h. Solid NH_4Cl (10 g) was added to the cooled solution, 15 min later 200 ml of water was added cautiously, and the solution was acidified with concentrated HCl. The phases were separated, and the aqueous phase was extracted with three portions of ether. The combined organic phases were extracted with two 200-ml portions of 1 N HCl, two 200-ml portions of 5% $NaHCO_3$, and 200 ml of saturated NaCl, dried ($MgSO_4$), and concentrated on a rotary evaporator. GLC analysis at 200 °C using *n*-$C_{17}H_{36}$ as an internal standard showed a 3.9% yield of phenylcyclopentadiene (3) identified as described in the CpNa reaction which follows. Several small peaks of retention time similar to that of benzonorbornadiene (4) were observed, but were proven not to be 4 by GLC–mass spectrometry.

Cyclopentadienylsodium (1b) and Benzyne. A solution of 6.6 g (0.10 mol) of cyclopentadiene in 25 ml of THF was added dropwise with stirring to 8.19 g (0.21 mol) of sodium amide in 35 ml of THF at 25°. After stirring for 1 h the mixture was heated to reflux, and 11.25 g (0.10 mol) of chlorobenzene in 30 ml of THF was added dropwise over a period of 45 min. Reflux was maintained for 1 h more, the mixture was neutralized with 12 g of solid NH_4Cl, and 2 h later water was added cautiously. The mixture stood overnight. After acidification with HCl the phases were separated and the aqueous phase was extracted with three portions of ether. The combined organic phases were extracted with two 200-ml portions of 1 N HCl, two 200-ml portions of 5% $NaHCO_3$, and 200 ml of saturated NaCl and dried ($MgSO_4$). The ether was removed on a rotary evaporator. Addition of CCl_4 to the residual oil gave 0.27 g of red-brown precipitate which was recrystallized from ethanol to yield 0.23 g (1.06 mmol, 2.1%) of 1,4-diphenylcyclopentadiene: mp 155–159 °C (lit. mp 156,[27a] 158–158.5,[27b] 155.5–157 °C[27c]); ir (KBr) 3070 (m), 1500 (m), 1452 (m), 920 (m), 754 (s), and 695 cm^{-1} (s); mass spectrum (70 eV) *m/e* (rel intensity) 220 (2), 219 (19), 218 (100), 217 (27), 216 (7), 215 (19), 203 (16), 202 (26), 115 (14); calcd for $C_{17}H_{14}$, (P + 1)/P = 18.7%, (P + 2)/P = 1.75%. The ^1H NMR spectrum agreed with that in the literature.[27c]

The CCl_4 filtrate was distilled and 1.41 g (9.92 mmol, 9.9%) of phenylcyclopentadiene (3) was collected at 115–120 °C (0.2 Torr) [lit. bp 73 °C (5 Torr),[26] 180–220 °C (760 Torr)[28]]. Neat liquid **3** dimerized or polymerized upon standing overnight. A pure sample was obtained by preparative GLC at 230°: ^1H NMR ($CDCl_3$) δ 3.05 (m), 3.23 (d, *J* = 1.2 Hz), 6.08 (m), 6.33 (m), 6.48 (m), 6.75 (m), 7.0–7.5 (broad m). The relative peak areas at 3.05–3.23, 6.08–6.75, and 7.0–7.5 were 2:3:5. The relative peak areas at 3.05 and 3.23 were 4:3, tentatively assigned to the methylene protons of 2-phenylcyclopentadiene and 1-phenylcyclopentadiene, respectively. This ^1H NMR spectrum agrees with a previous report.[26] Mass spectrum (70 eV) *m/e* (rel intensity) 143 (53), 142 (94), 141 (100), 116 (20), 115 (98), 89 (25), 69.5 (33), 57.6 (26), 51 (23), 38 (35).

Anal. Calcd for $C_{11}H_{10}$: C, 92.91; H, 7.09. Found: C, 92.76; H, 6.99. The distillation residue was dissolved in dichloromethane and filtered through a short silica gel column. Distillation of solvent left an oil which was crystallized from methylene chloride–hexane to give 0.16 g (0.348 mmol, 1.7%) of 1,2,3,4,5-pentaphenylcyclopentadiene: mp 243–254 °C (lit. mp 244–246,[29a] 258–259 °C[29b]); ^1H NMR ($CDCl_3$) δ 4.90 (s, 1 H), 6.9–7.4 (broad m, 25 H); mass spectrum (70 eV) *m/e* (rel intensity) 448 (7), 447 (40), 446 (100), 420 (35), 291 (18); calcd for $C_{35}H_{26}$, (P + 1)/P = 38.5%, (P + 2)/P = 7.41%. Its ir spectrum agreed with that in the literature.[29c]

Cyclopentadienylpotassium (1c) and Benzyne. Potassium amide was prepared from 4.3 g (110 mg-atoms) of potassium, a trace of ferric chloride hexahydrate, and ca. 150 ml of liquid ammonia in the usual manner.[30] The ammonia was evaporated and replaced with 40 ml of THF. A solution of 3.3 g (50 mmol) of cyclopentadiene in 10 ml of THF was added dropwise, producing a white precipitate, and the mixture was allowed to stand for 1 h. Upon heating to reflux, most of the precipitate dissolved, and a solution of 5.63 g (50.0 mmol) of chlorobenzene in 15 ml of THF was added dropwise over a period of 45 min. The remainder of the procedure was identical with that described for **1a**. GLC analysis at 185 °C showed no trace of benzonorbornadiene, and at 200 °C using *n*-$C_{16}H_{34}$ as an internal standard, the yield of phenylcyclopentadienes was determined to be 0.9%.

Cyclopentadienylmagnesium Chloride (1d) and Benzyne with HMPA. A mixture of 0.97 g (40.0 mg-atoms) of magnesium turnings, 6.5 ml of 3.1 M ethylmagnesium chloride in ether (20.2 mmol), 1.32 g (20.0 mmol) of cyclopentadiene, and 10 ml of THF was stirred at 25 °C for 30 min until ethane evolution subsided, and refluxed for 2.5 h. An aliquot was examined by ^1H NMR to confirm the absence of unreacted cyclopentadiene. The mixture was cooled, 7.35 g (41.0 mmol) of HMPA was added, the mixture was brought to reflux, and a solution of 3.5 g (20.0 mmol) of o-bromofluorobenzene in 7.35 g (41.0 mmol) of HMPA was added dropwise over a period of 45 min. The mixture was refluxed for 1 more h and cooled to 25 °C and 20 ml of 99.8% D_2O was added. After standing overnight the solution was acidified with concentrated HCl, and an ether solution was prepared for GLC analysis by the procedure used for the reaction of **1a**. A 1.1% yield of phenylcyclopentadiene was determined by GLC at 200° using *n*-$C_{17}H_{36}$ as an internal standard. The yield of benzonorbornadiene (4) was determined similarly at 185 °C to be 0.24%. Although several peaks (<1%) of similar retention time to benzonorbornadiene (4) were observed, the correct identification of 4 was confirmed by a programmed GLC–mass spectrometry run from 90 to 260 °C at 4 °C/min. The mass spectrum assigned to benzonorbornadiene (4) showed 100% monodeuteration by analogy to the spectrum of an all-protio sample reported[31] assuming the P − 1 peak arises from loss of a hydrogen or deuterium atom from the 7 position with no deuterium isotope effect. Mass spectrum (70 eV) *m/e* (rel intensity) 144 (11), 143 (89), 142 (100), 141 (42), 140 (10), 117 (19), 116 (42).

5-Trimethylstannylcyclopentadiene (1f)[32] was prepared from cyclopentadiene and diethylaminotrimethylstannane:[33] bp 64.5–68.0 °C (9–10 Torr) [lit. bp 38 (3 Torr),[32] 85 °C (10 Torr)[34]]. Because **1f** formed a white powder upon exposure to air, it was stored and used under dry nitrogen.

5-Trimethylstannylcyclopentadiene (1f) and Benzyne. To 0.49 g (20.0 mg-atoms) of magnesium turnings, 2.24 g (9.8 mmol) of **1f**, and 5 ml of THF at reflux a solution of 1.75 g (10.0 mmol) of o-bromofluorobenzene in 5 ml of THF was added dropwise over a period of 15 min. Reflux was continued for 1 h. A tarry precipitate formed upon the addition of ether. The ether solution was decanted, and a portion of it was used to determine the yields of benzonorbornadiene (4, 3.6%) and o-fluorotrimethylstannylbenzene (5, 32.1%) by GLC relative to *n*-$C_{14}H_{30}$ at 180 °C. The yield of *anti*-7-trimethylstannylbenzonorbornadiene (2, M = *anti*-$SnMe_3$, 1.9%) was determined relative to *n*-$C_{15}H_{32}$ at 200 °C. Another portion of the ether solution was separated into two components by preparative GLC at 250 °C. The shorter retention time component was a mixture of 4 (4.55% by weight, 8.3 mol %) and 5 (the remainder) by GLC analysis at 160 °C. This mixture could not be separated conveniently by preparative GLC. ^1H NMR (CCl_4) showed the expected multiplets for 4[35] and δ 0.48 (s, 9 H, *J* = 55 Hz for ^{117}Sn and ^{119}Sn satellites[36]) and 6.9–7.6 (m, 4 H) for 5. Ir (film) 3060 (w), 2975 (m), 2915 (w), 1595 (m), 1465 (s), 1460 (s), 1435 (s), 1258 (m), 1200 (s), 1190 (s), 1105 (m), 1055 (m), 824 (m), 814 (m), 755 (s), and 727 cm^{-1} (m). GLC–mass spectra (70 eV) showed the expected spectra for 4[31] and for 5: *m/e* (rel intensity) 260 (0.96), 258 (0.67), 245 (100), 243 (74), 241 (45), 239 (2), 237 (3), 227 (18), 225 (13), 223 (8), 215 (13), 213 (10), 211 (7), 210 (13), 208 (9), 206 (5), 197 (7), 195 (5), 193 (3), 169 (8), 167 (6), 165 (4), 139 (35), 137 (26), 135 (23), 96 (5), and 95 (2).

Anal. Calcd for $C_9H_{13}FSn$ with 8.3 mol % $C_{11}H_{10}$: C, 45.67; H, 5.22. Found: C, 45.73, H, 5.21.

The longer retention time component isolated by preparative GLC was *anti*-7-trimethylstannylbenzonorbornadiene: ^1H NMR (CCl_4) δ 0.13 (s, 9 H, *J* = 51 Hz for ^{117}Sn and ^{119}Sn satellites[36]), 2.58 (m, 1 H), 4.01 (m, 2 H) 6.78–7.20 (m, 6 H). Irradiation at δ 2.58 sharpened the upfield portion of the δ 6.78–7.20 multiplet, and irradiation at δ 6.80 simplified δ 2.58 to a triplet (*J* = 2.4 Hz), establishing δ 2.58 as a syn-7 proton.[8–10] Ir (film) 3060 (m), 2965 (m), 2900 (m), 1453 (m), 1440 (m), 1190 (m), 843 (m), 758 (s), and 695 cm^{-1} (s). GLC–mass spectrum (70 eV) *m/e* (rel intensity) 306 (5), 304 (4), 302 (2), 291 (72), 289 (74), 287 (59), 265 (32), 263 (24), 261 (21), 165 (31), 163 (34), 161 (15), 141 (95), and 115 (100).

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Registry No.—**1a**, 16733-97-4; **1b**, 4984-82-1; **1c**, 30994-24-2; **1d** (X = Cl), 34766-85-3; **1f**, 2726-34-3; *anti*-**2f**, 57496-94-3; **3** 1-phenyl isomer, 1961-98-4; **3** 2-phenyl isomer, 2327-56-2; **4**, 4453-90-1; 5, 2542-07-6; benzyne, 462-80-6; sodium amide, 7782-92-5; 1,4-diphenylcyclopentadiene, 57496-95-4; 1,2,3,4,5-pentaphenylcyclopentadiene, 2519-10-0; potassium amide, 17242-52-3; ethylmagnesium chloride, 2386-64-3; diethylaminotrimethylstannane, 1068-74-2; cyclopentadiene, 542-92-7.

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Highly Stereoselective Preparations of *anti*-7-Benzonorbornadienyl Grignard Reagents

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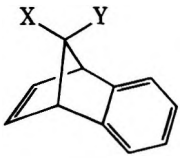
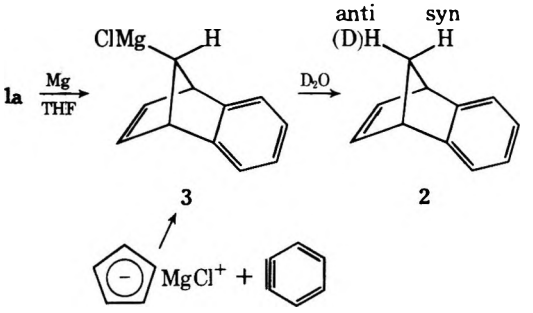
Grignard reagents have been prepared in tetrahydrofuran from *anti*- and *syn*-7-chlorobenzonorbornadiene (*anti*-Cl and *syn*-Cl) and *anti*- and *syn*-7-bromobenzonorbornadiene (*anti*-Br and *syn*-Br) by three methods: reaction with magnesium turnings, reaction with activated magnesium prepared by reduction of magnesium halide with potassium metal, and reaction with sodium naphthalenide (NaNaph) in the presence of magnesium halide. Deuterolyses of the Grignard solutions give deuterated benzonorbornadiene (**2**) with >85% overall retention of configuration from *anti*-Cl and *anti*-Br by the magnesium metal methods. Carbonation of the Grignard reagent from *anti*-Br and magnesium turnings also proceeds with high overall retention of configuration. The stereoselectivity does not depend on particle size or purity of the magnesium. In contrast, *syn*-Cl and *syn*-Br give deuterated **2** by the same methods with little or no stereoselectivity. The NaNaph method gives little stereoselectivity with any of the substrates but produces the Grignard reagents in higher yields. Sizable amounts of undeuterated benzonorbornadiene are formed in all of the preparations using magnesium turnings or activated magnesium. Grignard reagent formation and deuterolysis with *anti*-7-bromobenzonorbornene (**5**) also proceed with high retention of configuration. The Grignard reactions at saturated carbon with *anti*-Br, *anti*-Cl, and **5** are far more stereoselective than any previously reported. The results are discussed in terms of a mechanism of Grignard formation which proceeds by rate-limiting electron transfer to give a radical intermediate bound to the magnesium surface.

Both reaction of *anti*-7-chlorobenzonobornadiene (**1a**) with magnesium turnings in tetrahydrofuran (THF)[2] and cycloaddition of benzyne to the cyclopentadienyl Grignard reagent in THF[3] followed by deuterolysis give benzonorbornadiene-7-*d* (**2**) with the D incorporated >90% stereoselectively anti. Assuming that deuterolysis proceeds with retention of configuration,[4] both preparations must lead to the *anti*-7-benzonorbornadienyl Grignard reagent (**3**).

Three possible reasons for the stereoselectivity of these reactions are: (1) Both proceed stereoselectively to form **3**, and **3** is configurationally stable under the preparation and trapping conditions. (2) Both **3** and its syn isomer are formed but



1a, X = Cl; Y = H; *anti*-Cl
b, X = H; Y = Cl; *syn*-Cl
c, X = Br: Y = H; *anti*-Br
d, X = H; Y = Br; *syn*-Br

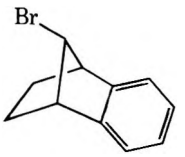


the mixture equilibrates rapidly to >90% **3**, which is then captured by deuterolysis. (3) Both **3** and its syn isomer are formed, but the syn Grignard reagent is rapidly destroyed under the reaction conditions. The third possibility would require that the isomeric Grignard reagents interconvert slowly or not at all during the time required to prepare them.

Previous studies of Grignard reagents show that the configurational stabilities are highly dependent on structure. Some acyclic primary Grignard reagents undergo configurational inversion on the NMR time scale at room temperature.[9] The tertiary Grignard reagent from optically active 1-bromo-1-methyl-2,2-diphenylcyclopropane (**4**) is configurationally stable for ≥30 min in refluxing di-*n*-butyl ether.[6] *endo*-2-Norbornylmagnesium bromide reverts to an equilibrium endo/exo mixture in ≤24 h in ether at room temperature.[5] A variety of secondary Grignard reagents fail to show inversion at ≥120 °C on the NMR time scale.[9a,10] On the other hand, Δ^3-cyclohexenylmagnesium bromide and Δ^3-cyclopentenylmagnesium bromide undergo rapid inversion on the NMR time scale at 25 °C in THF, presumably by a reversible homoallyl–cyclopropylcarbinyl rearrangement.[11]

The first possibility is most interesting because never before has any Grignard reagent been prepared with such high stereoselectivity at saturated carbon. The Grignard reagents from **4** and the corresponding chlorocyclopropane have been prepared and carbonated. The carboxylic acid obtained from bromide **4** had 59% retained and 41% inverted configuration, and that obtained from the corresponding chloride had 62.5% retained and 37.5% inverted configuration.[6] All other Grignard preparations from alkyl halides and magnesium have led to equilibrium mixtures of isomers. The loss of configuration has been established clearly in the cases of **4**[6] and the *exo*- and *endo*-2-bromonorbornanes[5] to occur during the Grignard formation step, not during subsequent deuterolysis or carbonation. Stereoselectivity of ≥90% has been reported for Grignard preparations from vinyl bromides such as the β-bromostyrenes, 1-bromopropenes, and 1-bromo-1-hexenes.[7,8]

In this paper we report details of Grignard preparations from *anti*-Cl, *syn*-7-chlorobenzonorbornadiene (**1b**), and the corresponding *anti*- and *syn*-7-bromobenzonorbornadienes (**1c,d**) by a variety of methods. The results clearly establish that stereoselective production of 2-*anti*-7-*d* is due to the first possibility, stereoselective formation of Grignard reagent **3**. To learn more about the mechanism of this unprecedented stereoselective Grignard reaction we have also tested effects of the state and purity of the magnesium metal on the reaction, thermal stabilities of the Grignard reagents, equilibration of the *anti*- and *syn*-7-carbomethoxybenzonorbornadienes, and preparation of the Grignard reagent from *anti*-7-bromobenzonorbornene (**5**).

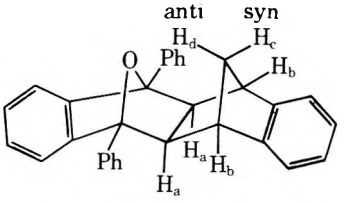


5

Previous attempts to prepare and carbonate Grignard reagents from **1c**[12] and **5**[13] led to poor yields of carboxylic acids and considerable 7,7′-dimer formation. Earlier experience with **3** formed by cycloaddition indicated that deuterolysis was a much more effective trapping method than carbonation,[3b] so we chose to trap the Grignard reagents prepared from **1a–d** and **5** by deuterolysis.

Results

Three methods were employed to prepare Grignard reagents from **1a–d.** (1) The alkyl halide was added to a refluxing THF solution over ordinary magnesium turnings. (2) Activated magnesium was prepared from anhydrous magnesium halide and potassium metal in THF,[14] and the alkyl halide was added to the resulting mixture. (3) A 0.7–0.9 M THF solution of 2.3 equiv of sodium naphthalenide (NaNaph) was added to a solution of 1.0 equiv of the alkyl halide and 1.3 equiv of anhydrous magnesium halide at room temperature.[15] All three procedures were completed by deuterolysis of the Grignard reagent, determination of yield and purification of benzonorbornadiene (**2**) by GLC, and conversion of **2** to its diphenylisobenzofuran Diels–Alder adduct **6**.[16]



6

Deuterium analyses of **6** were performed by low eV mass spectrometry for total deuterium content and by ^{1}H NMR for both amount and location of deuterium. Because of low deuterium incorporation in many experiments, the ^{1}H NMR results were determinations of small differences in areas of large proton signals and are reliable only to ±0.05 atom D at each isomeric position (anti or syn). Usually the total deuterium found by ^{1}H NMR at the two positions agreed within ±0.08 atom D with the mass spectra. Complete results are in Table I. To check the accuracy of the ^{1}H NMR results, four representative samples were analyzed by Fourier transform deuterium NMR at 33.77 MHz with the help of Professor L. K. Montgomery at Indiana University. No internal standard was used in the deuterium NMR analyses, so only relative amounts of anti and syn D were obtained. Use of mass spectral results for total D and deuterium NMR for location of D gave the analyses in the last two columns of Table II, which agree well with the ^{1}H NMR analyses.

Numerous attempts to trap the Grignard reagents with electrophiles other than D_2O were disappointing. No simple derivatives were isolated after treatment with chlorotrimethylsilane, dimethyl sulfate, ethyl chloroformate, *N*-chlorosuccinimide, methyl iodide, benzaldehyde, acetic anhydride, or ethyl bromoacetate. Carbonation produced the expected carboxylic acids in much lower yield than deuterolysis produced **2**. Oxidation with O_2 of the Grignard reagent **3** from cycloaddition of benzyne and CpMgBr gave only a 4%

Table I. Stereochemistry of Formation and Deuterolysis of 7-Benzonorbornadienyl Grignard Reagents in THF

Expt no.	Reactant	Reagents	Temp, °C	Time, h	% yield of 2	Atom excess D in 6		
						By ^{1}H NMR[a]		
						Anti	Syn	By MS
1[b]	C_5H_5MgBr	Benzyne	65	1.0	29	0.91	0.00	0.91
2	*anti*-Cl	Mg turnings	65	20	86	0.56	0.05	0.68
3	*anti*-Cl	Mg turnings[c]	70	24	56	0.47	0.00	0.53
4	*anti*-Cl	$MgCl_2$/NaNaph	25	0.25	95	0.31	0.25	0.59
5	*anti*-Cl	$MgCl_2$/NaNaph	25	0.25	92	0.39	0.30	0.72
6	*anti*-Cl	NaNaph	25	0.25	66	0.00	0.00	−0.02
7	*anti*-Cl	Mg turnings[d]	65	23	81	0.39	0.07	0.49
8	*anti*-Cl	$MgCl_2$/NaNaph[e]	65	24	70	0.00	0.00	0.03
9	*anti*-Cl	$MgCl_2$/NaNaph[e]	65	24	71	0.00	0.02	0.13
10	*anti*-Cl	Activated Mg	25	780		No reaction		
11	*syn*-Cl	Mg turnings	65	4	41	0.00	0.00	0.08
12	*syn*-Cl	Mg turnings	65	15	47	0.24	0.16	0.39
13	*syn*-Cl	Activated Mg	65	20	41	0.11	0.05	0.08
14	*syn*-Cl	$MgCl_2$/NaNaph	25	0.25	36	0.64	0.33	0.86
15	*syn*-Cl	$MgCl_2$/NaNaph	25	0.25	32	0.63	0.18	0.91
16	*anti*-Br	Mg turnings	65	0.017	67	0.19	0.00	0.20
17	*anti*-Br	Mg turnings	65	0.5	73	0.24	0.07	0.28
18	*anti*-Br	Mg turnings	65	4	74	0.23	0.04	0.29
19[f]	*anti*-Br	Mg turnings	65	0.083	72	0.24	0.06	0.30
			65	0.5	75	0.25	0.00	0.28
			65	4	71	0.15	0.00	0.23
			65	10	66	0.11	0.01	0.09
			65	20	65	0.01	0.00	0.00
20[f]	*anti*-Br	Mg turnings	65	0.5	74	0.30	0.05	0.37
			25[g]	0.1	77	0.25	0.08	0.33
21	*anti*-Br	Activated Mg	25	6.33	82[h]	0.25	0.05	0.28
22[f]	*anti*-Br	Activated Mg	25	6.33	74	0.28	0.11	0.36
			65	4	70	0.25	0.09	0.30
23[f]	*anti*-Br	Activated Mg	25	7	72	0.21	0.00	0.21
			65	20	58	0.01	0.01	−0.01
24[f]	*anti*-Br	Activated Mg	25	3.83	60	0.25	0.03	0.28
			65	4	66	0.10	0.00	0.18
			65	20	49	0.00	0.00	0.00
25[f]	*anti*-Br	Sublimed Mg	65	0.083	76	0.28	0.04	0.38
			65	4	80	0.27	0.07	0.36
			65	20	67	0.05	0.01	0.07
26	*anti*-Br	$MgBr_2$/NaNaph	25	0.25	85	0.30	0.29	0.60
27[f]	1*syn*-Br	Mg turnings	65	0.25	60	0.08	0.02	0.10
			65	0.75	68	0.19	0.23	0.38
			65	4.25	71	0.10	0.06	0.13
28[f]	*syn*-Br	Activated Mg	25	2.25	72	0.25	0.15	0.37
			65	0.5	68	0.23	0.15	0.35
			65	4	68	0.21	0.13	0.30
29	*syn*-Br	Activated Mg	25	20.5	37	0.00	0.00	−0.01
30	*anti*-Br	Mg turnings[i]	65	0.5	90	0.01	0.02	0.01
31[f]	*anti*-Br	Mg turnings[j]	65	0.5	76	0.72	0.21	0.95
			65	240	31	0.14	0.08	0.21
32	*anti*-Br	Mg turnings[i]	65	0.5	59	0.01	0.00	0.02

[a] Estimated error ±0.05 atom excess D. [b] Reference 3. [c] The solvent was 7-oxabicyclo[2.2.1]heptane instead of THF. [d] The solution was treated with NaNaph at 25 °C for 0.25 h before deuterolysis. [e] The reaction with NaNaph was carried out at 25 °C for 0.25 h before heating to reflux. [f] Aliquots were withdrawn from a single reaction mixture at the times indicated. [g] Reaction mixture from preceding line was cooled to 25 °C and 3.65 equiv of HMPA was added. [h] Estimated yield ±10%, no internal standard. [i] THF-d_8, hydrolyzed with H_2O. [j] THF-d_8. Aliquot at 0.5 h was hydrolyzed with D_2O. Remainder at 240 h was hydrolyzed with H_2O.

yield of *anti*-7-benzonorbornadienol which required a tedious chromatography for purification.

Reactions of *anti*-Br and *anti*-Cl with magnesium turnings in refluxing THF followed by deuterolysis immediately after the starting halide was consumed gave benzonorbornadiene (**2**) in about 70 and 86% yields, respectively. However, the **2** was only partly deuterated, 27% D from *anti*-Br (average of expt 16–20) and 68% D from *anti*-Cl (expt 2). If the yield of Grignard reagent is equal to the yield of benzonorbornadiene-*d* [(% yield of **2**) × (atom excess D in **2** determined by mass spectrometry)], *anti*-Br and *anti*-Cl gave 20 and 58% yields of Grignard reagent, respectively. The higher yield of Grignard reagent from the alkyl chloride is consistent with previous reports of the 1-halo-1-methyl-2,2-diphenylcyclopropanes.[6] Complete consumption of *anti*-Cl required 20 h at reflux, while all of the *anti*-Br usually reacted in 0.5 h. Prolonged reflux of the Grignard solutions from *anti*-Br led to still smaller degrees of deuteration of **2** but only a slight

Table II. Comparison of ^1H NMR and ^2H NMR Analyses of 6

	Atom excess D in 6			
	By ^1H NMR		By ^2H NMR	
Expt	Anti	Syn	Anti	Syn
2	0.56	0.05	0.60	0.08
12	0.24	0.16	0.23	0.16
24	0.25	0.03	0.25	0.03
28	0.25	0.15	0.22	0.15

decrease in the yield of 2 (expt 19). This indicates that much of the Grignard reagent which disappeared from the solution was converted to undeuterated 2, either by reaction with adventitious moisture or by reaction with THF. The deuterium in 2 from *anti*-Br averaged 86% anti, and from *anti*-Cl was >90% anti even after 20 h at reflux. Since prolonged reflux of the solutions from *anti*-Br destroyed both anti and syn Grignard reagents (expt 19), the experiments with the shortest reflux times (0.5 h or less) are the best indicators of the stereoselectivity of Grignard formation. In an attempt to prepare a Grignard reagent from *anti*-Cl with activated magnesium, no reaction occurred at 25 °C (expt 10). Activated magnesium did enable preparation of Grignard solutions from *anti*-Br at 25 °C with essentially the same stereoselectivity as magnesium turnings gave at 65 °C (expt 22–24). Use of turnings from Dow sublimed magnesium crystal gave the same results as the ordinary grade of magnesium (expt 25).

Often hexamethylphosphoramide (HMPA) greatly increases the reactivity and ionic character of organomagnesium compounds.[17] In expt 20 a Grignard solution prepared from *anti*-Br and magnesium turnings was treated with 3.65 equiv of HMPA at 25 °C for 0.1 h before deuterolysis. No change in yield and only a slight decrease in stereoselectivity of deuteration in 2 resulted.

Reactions of *anti*-Br and *anti*-Cl with NaNaph and anhydrous magnesium halides (expt 4, 5, 26) gave better yields of Grignard reagents than reactions with magnesium metal. Presumably the Grignard reagent is formed by an electron transfer–transmetalation sequence.[18]

$$RX + Na^+Naph\cdot^- \rightarrow R\cdot + Naph + NaX$$

$$R\cdot + Na^+Naph\cdot^- \rightarrow RNa + Naph$$

$$RNa + MgX_2 \rightarrow RMgX + NaX$$

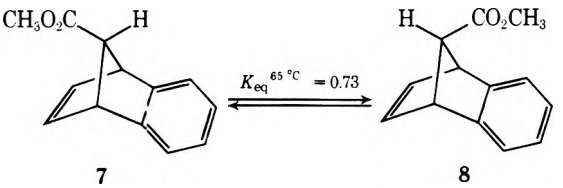
That an organomagnesium rather than an organosodium species reacts with D_2O is shown in expt 6, where NaNaph treatment of *anti*-Cl in the absence of $MgCl_2$ led to a lower yield of 2 which contained no deuterium. The NaNaph/MgX_2 reactions usually gave 2 with only a small excess of *anti-d* over *syn-d*. The lack of selectivity occurs during Grignard formation and is not due to isomerization of a more stereoselectively formed Grignard reagent by excess NaNaph, because treatment of a preformed Grignard reagent from *anti*-Cl and magnesium turnings with NaNaph still allowed highly stereoselective formation of 2-*anti*-7-*d* (expt 7). Unlike the Grignard reagent from *anti*-Cl and magnesium turnings, the one from NaNaph/$MgCl_2$ did not survive in refluxing THF (expt 8, 9).

Treatment of *syn*-Cl with magnesium turnings gave much lower yields of benzonorbornadiene than the corresponding reaction of *anti*-Cl, and much less deuterium was incorporated (expt 11, 12). Although the two experiments gave widely different degrees of deuteration, there was little stereoselectivity. *syn*-Cl also reacted with activated magnesium at 65 °C (expt 13) with about the same yield and extent of deuteration as with magnesium turnings. With NaNaph/$MgCl_2$ *syn*-Cl gave only 32–36% of 2 which was about 90% deuterated with more D anti than syn (expt 14, 15).

syn-Br behaved still differently from the other halides. With either Mg turnings at reflux or activated Mg at room temperature it gave about 70% of 2 which contained a total of 0.37 atom excess D distributed about equally between the syn and anti positions (expt 27, 28). An attempted Grignard preparation from *syn*-Br and activated Mg which required 20.5 h at 25 °C gave completely undeuterated 2 (expt 29). Experiment 27 gave a higher degree of deuteration after 0.75 h than after 0.25 h, probably because freshly formed Grignard reagent consumed a small amount of adventitious water in the first few minutes of the reaction to give undeuterated 2. Since expt 27 is the only one where an increase in deuterium content was found in two successive samples, adventitious water does not appear to be a problem in the other experiments where the Grignard solution was sampled at different times.

The source of the undeuterated benzonorbornadiene is not known in the reactions of benzonorbornadienyl halides with magnesium turnings or activated magnesium followed by deuterolysis. The reproducibility of the atom excess D in 2 from nine experiments which varied in scale from 0.25 g to 2.25 g of *anti*-Br demonstrates that hydrolysis by H_2O was not a major source of undeuterated 2. Since the most likely source of hydrogen was the THF, Grignard reagents were prepared in THF-d_8. In expt 30 and 31 two samples of the same lot of THF-d_8 were dried over sodium metal and used to prepare Grignard reagent from magnesium turnings and *anti*-Br under identical conditions. One Grignard solution was hydrolyzed with H_2O (expt 30) and part of the other was hydrolyzed with D_2O (expt 31). The remainder of the second solution was refluxed for 10 days and then hydrolyzed with H_2O. Surprisingly the benzonorbornadiene recovered after hydrolysis contained only 0.01 atom excess D while that recovered after deuterolysis contained 0.95 atom excess D. Continued reflux of the Grignard solution of expt 31, conditions known to destroy the Grignard reagent, led to a much lower yield of 2 which contained 0.21 atom excess D, indicating that most of the D in the portion deuterolyzed after 0.5 h came from the D_2O. Because of the apparent anomaly of expt 30, it was repeated (expt 32) with a new batch of THF-d_8 which was purified by distillation from the sodium ketyl of benzophenone. Although the yield of 2 was lower in expt 32 than in expt 30, the deuterium content was the same within experimental error by both mass spectrometry and ^1H NMR analyses.

In expt 20 samples of the Grignard solution were poured onto solid CO_2 before and after HMPA was added to the THF solution. The resulting mixtures of carboxylic acids were converted to mixtures of *anti*- and *syn*-7-carbomethoxybenzonorbornadiene (7 and 8). Without HMPA a 10.3% yield



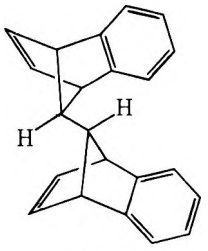
7 8

of carboxylic acids was isolated and the mixture of esters was 87% 7 by GLC, the same as the anti/syn distribution of deuterolysis products (Table I). With HMPA a 6.5% yield of carboxylic acids was isolated and the ester mixture was 75% 7 by GLC, also within experimental error of the deuterolysis results. Yields of benzonorbornadiene-*d* from deuterolysis were 27 and 25%, respectively, much better than the yields of carboxylic acids.

To establish the structures of 7 and 8, anti ester 7 was syn-

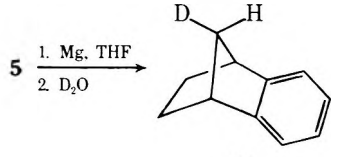
thesized stereospecifically by treatment of *anti*-Br with *sec*-butyllithium in hexane at −78 °C followed by carbonation and esterification in 17.6% overall yield after preparative GLC isolation. Its structure was proven by the characteristic four-bond coupling of 0.35 Hz between the syn-7 proton and the vinyl protons in its ^{1}H NMR spectrum.[19] Treatment of **7** in refluxing 0.4 M sodium methoxide in 80/20 (v/v) methanol/HMPA produced an equilibrium mixture of 58% **7** and 42% **8**. The ^{1}H NMR spectrum of **8** showed no coupling between the anti-7 proton and the vinyl protons.

In expt 21 we attempted to isolate and identify the side products from reaction of *anti*-Br with activated magnesium. The unsymmetrical dimer **9** was obtained in 5.7% yield by silica gel chromatography, but no other compounds could be isolated in a form suitable for identification.



9

To test whether the C_2–C_3 double bond of *anti*-Br and *anti*-Cl is a structural requirement for highly stereoselective Grignard formation, *anti*-7-bromobenzonorbornene (**5**) was treated with magnesium turnings in refluxing THF, and the mixture was hydrolyzed with D_2O. A 79% yield of benzonorbornene (**10**) was purified by GLC and analyzed by mass



10

spectrometry to contain 0.40 atom excess D. A 220-MHz ^{1}H NMR spectrum of **10**, in which the *anti*- and *syn*-7 proton resonances were clearly resolved from all other multiplets, showed 0.38 ± 0.05 atom excess D anti and 0.00 ± 0.05 atom excess D syn. This stereoselectivity is as high as or higher than in Grignard formation from *anti*-Br or *anti*-Cl.

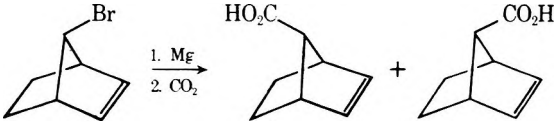
Discussion

anti-Br, *anti*-Cl, and *anti*-7-bromobenzonorbornene (**5**) react with magnesium with high retention of configuration. Under similar conditions *syn*-Br and *syn*-Cl give mixtures of *anti* and *syn*-7-benzonorbornadienyl Grignard reagents in which the syn Grignard reagent neither isomerizes rapidly to its anti isomer nor is selectively destroyed. Therefore, the formation of Grignard reagents from *anti*-Br, *anti*-Cl, and **5** and the cycloaddition of benzyne to cyclopentadienyl Grignard reagents are kinetically controlled. *anti*-Br, *anti*-Cl, and **5** react with magnesium and deuterolyze to produce benzonorbornadiene-7-*d* with at least a 6.1/1.0 preference for retention of configuration (based on expt 16–20). Only with vinyl bromides has such high stereoselectivity been observed before.[7,8] The only other Grignard preparations from halides and magnesium at saturated carbon known to proceed stereoselectively gave a maximum retention/inversion ratio of 1.67.[6]

In refluxing THF Grignard reagents from *anti*-Br start to decompose in less than 4 h and are completely consumed in 20 h. The thermal stability of the Grignard reagent from *anti*-Cl has not been tested directly, but it must be more stable than that from *anti*-Br because its formation required 20 h in refluxing THF. The data in Table I indicate that the configurational stabilities of the Grignard reagents from *anti*-Br must be at least as great as their thermal stabilities. Thus they are at least comparable in configurational stability to many secondary Grignard reagents studied previously.[5,9a,10] They do not invert configuration rapidly by homoallyl-cyclopropylcarbinyl rearrangement as Δ^3-cyclohexenyl- and Δ^3-cyclopentenylmagnesium halides do.[11]

Methyl esters **7** and **8** were designed to test the relative stabilities of anti- and syn-7-substituted benzonorbornadienes. Much greater stability of the anti isomer would help explain stereoselective formation of anti Grignard reagents. However, insofar as **7** and **8** are reasonable models for Grignard reagents, the anti isomer is only slightly favored at equilibrium.

We hypothesized at one time that the C_2–C_3 double bond of **3** could stabilize the anti Grignard reagent by coordinating to the magnesium atom more strongly than the benzene ring coordinates to magnesium in the syn Grignard reagent. However, such coordination is not a necessary feature for stereoselective Grignard formation because the saturated analogue **5** forms a Grignard reagent with as high retention of configuration as *anti*-Br and *anti*-Cl. Also treatment of *syn*-7-bromonorbornene (**11**) with magnesium in ether fol-



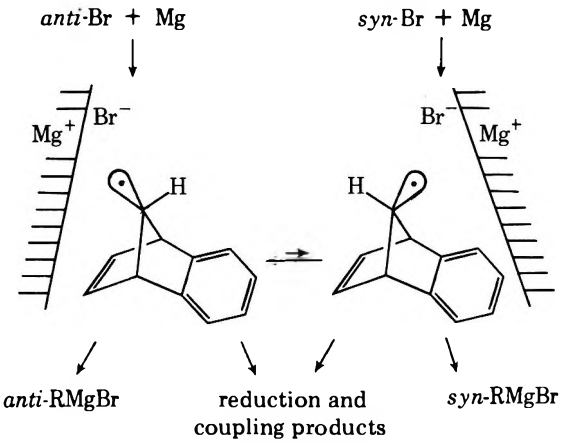
11 **2** : **1**

lowed by carbonation gives a 2/1 mixture of the corresponding anti and syn carboxylic acids.[20]

Since the origin of the stereoselectivity is kinetic, an explanation for our unusual results must lie in the mechanism of Grignard reagent formation. Diverse evidence supports a mechanism which proceeds by a free radical at the magnesium surface. For example, reaction of 1-chloro-2-methyl-2-phenylpropane with magnesium gives several products expected from free-radical rearrangement.[21] Grignard preparations from **1c**[12] and **5**[13] give substantial amounts of dimers from apparent free-radical coupling. Radical disproportionation and coupling account for the side products from treatment of 1-bromo-1-methyl-2,2-diphenylcyclopropane with magnesium in ether.[6] CIDNP in ^{1}H NMR spectra of alkyl Grignard reagents has been detected, but it must arise from coupling of free radicals in solution rather than at the magnesium surface.[22] The relative rates of reaction of alkyl halides with magnesium metal correlate better with their polarographic reduction potentials than with their rates of carbanion, SN2, lithium–halogen exchange, or tributyltin hydride reactions.[23] This suggests that the rate-limiting step is electron transfer from the metal to the alkyl halide.[23] Finally, the loss of configuration in formation of Grignard reagents at saturated carbon has long been cited as evidence for a radical intermediate. Radical surface mechanisms have been discussed recently by several authors.[6,22,23]

In spite of the high stereoselectivity, reactions of *anti*-Cl and *anti*-Br with magnesium may still proceed by a rate-limiting electron transfer to form a 7-benzonorbornadienyl radical at the magnesium surface as shown in Scheme I. This mechanism requires only that capture by magnesium of the anti surface-bound radical proceed faster than rearrangement to the syn surface-bound radical. Within the framework of Scheme I several experimental facts support stronger anti than syn binding to the magnesium surface: (a) *anti*-Br and *anti*-Cl react faster than *syn*-Br and *syn*-Cl, respectively. (b) *anti*-Cl gives much higher yields of deuterated benzonorbornadiene than *syn*-Cl. Yields from *anti*-Br and *syn*-Br are

Scheme I



about the same, however. (c) *syn*-Br and *syn*-Cl give approximately equal amounts of anti and syn Grignard reagents. The much faster reactions of the bromides than of the chlorides with magnesium also supports qualitatively a rate-limiting electron transfer step. A possible reason for stronger anti binding than syn binding of benzonorbornadienyl species to the metal is substantial steric hindrance between the benzene ring and the metal surface. On the other hand, highly stereoselective Grignard formation from *anti*-7-bromobenzonorbornene (**5**) and lack of stereoselectivity in reaction of *syn*-7-bromonorbornene (**11**)[20] suggest little difference in the abilities of ethano and etheno bridges of norbornene-like structures to bind to magnesium.

A radical mechanism for formation of 7-benzonorbornadienyl Grignard reagents must proceed at the metal surface rather than in solution. Tri-*n*-butyltin deuteride reductions of *anti*-Br and *syn*-Br, which proceed by a free-radical chain mechanism, give identical mixtures of 57% syn- and 43% anti-deuterated benzonorbornadiene.[16] Also, preparation of Grignard reagents by the NaNaph method proceeds via an alkyl free radical and perhaps an alkylsodium compound in solution.[18] Although the lifetimes of the 7-benzonorbornadienyl free radical and 7-benzonorbornadienylsodium under the NaNaph/MgX_2 conditions are not known, the lack of stereoselectivity in all such experiments in Table I must be due to rapid configurational inversion of one or both of them.

If *anti*-Br, *anti*-Cl, and **5** react with magnesium by the same mechanism as other alkyl halides, why do only they give high retention of configuration? We hypothesize that two major factors are involved.

First, the 7 position of benzonorbornadiene is strained. The average C_1–C_7–C_4 bond angle in norbornyl compounds studied by diffraction methods is 94°.[24] The ^{13}C–^1H coupling constants in the ^1H NMR spectrum of benzonorbornadiene are 134.6 and 136.2 Hz for the syn-7 and anti-7 protons, respectively,[25] which imply that the exocyclic carbon orbitals of the C–H bonds are $sp^{2.7}$ hybrids. Recent ESR studies suggest that 7-norbornenyl[26] and 7-benzonorbornadienyl[27] radicals are pyramidal rather than planar, presumably because of the high s character in the exocyclic carbon orbitals. The high s character should slow the rate of configurational inversion at C_7 in the 7-benzonorbornadienyl radical just as it causes high inversion barriers in analogous 7-azabenzonorbornadienes.[28] The inversion barrier cannot be high enough to prevent complete equilibration of the anti and syn radicals in solution, but it might still affect reaction of the radicals bound to a magnesium surface.

Second, there is a substantial difference in steric hindrance to approach of the anti- and syn-7 faces of benzonorbornadienyl halides to the magnesium surface. The argument that high s character slows configurational inversion of pyramidal radicals applies even better to Grignard formation from 1-bromo-1-methyl-2,2-diphenylcyclopropane (**4**) which proceeds with 18% retention of configuration.[6] However, the strengths of binding of the two enantiomeric pyramidal radicals from **4** to the metal are equal. Our hypothesis suggests that other alkyl halides which meet the requirements, (a) high s character in the carbon orbital of the carbon–halogen bond and (b) a substantial difference in hindrance to binding of the two isomers to the metal surface, may also form Grignard reagents with high retention of configuration.

The results of expt 30–32 in which Grignard reagents were prepared from *anti*-Br in THF-d_8 are most puzzling. Even though only about 0.02 atom excess D was incorporated into benzonorbornadiene using THF-d_8 and H_2O hydrolysis, THF still is the most intuitively likely source of hydrogen to account for the undeuterated **2** in THF/D_2O experiments. If this intuition is right, the results indicate a kinetic isotope effect of $\geq$60 for reaction of solvent with some intermediate benzonorbornadienyl species. Such a large isotope effect could occur only if hydrogen atom or proton transfer proceeded by a quantum mechanical tunneling mechanism, or by a multistep mechanism which would cause the experimental isotope effect to be a product of two or more primary kinetic isotope effects.

Experimental Section

General. Microanalyses were performed by J. Nemeth and associates. All temperatures, including melting points, are uncorrected. Infrared spectra were obtained either as a thin film between sodium chloride plates on Perkin-Elmer Model 137 or Model 237B instruments or as a potassium bromide pellet on Perkin-Elmer Model 521 or Beckman IR-12 instruments. Routine ^1H NMR spectra were obtained on Varian T-60, A-60A, A-56/60, or HA-100 spectrometers. The HA-100 equipped with a Hewlett-Packard Model 200ABR audio oscillator was used for decoupling experiments. Mass spectra were recorded on a Varian-MAT CH-5 mass spectrometer.

Analytical and Preparative GLC. Unless stated otherwise, analyses were performed with a 4 ft × 0.125 in. 20% Apiezon L on 60/80 Chromosorb W column at a He flow rate of 20 ml/min and 155 °C on a Hewlett-Packard Model 700 instrument equipped with a thermal conductivity detector. Naphthalene and *n*-tetradecane were used as internal standards. The thermal conductivity response factor per unit weight [(weight compd) (area standard)/(area compd) (weight standard)] of benzonorbornadiene (**2**) to naphthalene is 1.01, of **2** to n-$C_{14}H_{30}$ is 1.23, of *anti*-7-chlorobenzonorbornadiene (**1a**) to naphthalene is 1.19, and of *anti*-7-bromobenzonorbornadiene (**1c**) to naphthalene is 1.57. These response factors are averages of at least three determinations. The response factors of **1a** to n-$C_{14}H_{30}$ and **1c** to n-$C_{14}H_{30}$ calculated from these values are 1.45 and 1.91, respectively. The response factors of deuterated **2**, *syn*-Cl (**1b**), *syn*-Br (**1d**), and benzonorbornene are assumed to be the same as those for **2**, **1a**, **1c**, and **2**, respectively. Preparative GLC purifications of **2** were performed on a Varian Model A-90-P instrument at 200° on either a 0.25 in. × 10 ft 20% Apiezon L on 60/80 Chromosorb W column or a 0.375 in. × 10 ft 20% Apiezon L on 60/80 Chromosorb W column.

Materials. Unless noted otherwise Baker reagent grade magnesium turnings were washed with benzene and dried overnight under nitrogen at 120 °C, and tetrahydrofuran was distilled from the sodium ketyl of benzophenone just before use. Hexamethylphosphoramide, 1,2-dibromoethane, and 1,2-dichloroethane were distilled from calcium hydride under nitrogen. Tetrahydrofuran-d_8 was Merck Sharp & Dohme minimum 99% D, analyzed by mass spectrometry in our laboratory to contain 7% d_7 and 93% d_8 species. By ^1H NMR the residual protium was 21% at the α position and 79% at the β position. *anti*-7-Bromobenzonorbornadiene (**1c**),[12] *anti*-7-chlorobenzonorbornadiene (**1a**),[29] *anti*-7-bromobenzonorbornene (**5**),[13] and 7-oxabicyclo[2.2.1]heptane[30] were prepared by literature methods.

***syn*-7-Chlorobenzonorbornadiene (1b).** The literature method[31] for acetophenone-sensitized photolysis of *anti*-7-benzonorbornadienol after removal of solvent and evaporative distillation gave a 68% yield of a mixture of two compounds: the expected *exo*-tetracyclo[5.4.0.$0^{2,4}$.$0^{3,6}$]undeca-1(7),8,10-trien-5-ol and another tentatively identified as *syn*-7-benzonorbornadienol by similarity of ir and ^1H NMR spectral frequencies to those reported earlier.[31] Treatment of this mixture with thionyl chloride in ether by the literature method[31] gave a 47% yield of 1b after sublimation at 40–50 °C (0.03 Torr) and

recrystallization from hexane: mp 57.5–58.5 °C (lit.[32] mp 59.0–59.5 °C). Its ^{1}H NMR spectrum agreed with a previous report.[19c] Ir (KBr) 6.87 (m), 7.73 (m), 7.90 (m), 11.50 (m), 11.68 (m), 12.40 (s), 13.00 (s), 13.85 (m), and 14.53 μ (s).

***syn*-7-Bromobenzonorbornadiene (1d).** By a method suggested earlier[31,33] a solution of 5.16 g (23.4 mmol) of *anti*-Br and 500 mg of acetophenone in 250 ml of freshly distilled, nitrogen-purged benzene was photolyzed in a Rayonet reactor at 3500 Å for 360 h. The reaction was followed by ^{1}H NMR in which the 7-H of *syn*-Br appeared at δ 4.38 and the 7-H of *anti*-Br at δ 4.15. The solvent was removed under vacuum, and the resultant yellow oil was crystallized from petroleum ether (bp 30–60 °C). Recrystallization gave 1.91 g (8.65 mmol, 37.0%) of **1d**, mp 59.5–61.5 °C. Molecular distillation of the recrystallization mother liquors at 75–125 °C (0.5–0.6 Torr) followed by recrystallization from petroleum ether yielded an additional 0.59 g (2.67 mmol, 11.8%) of **1d**, mp 57–59 °C (lit.[34] mp 61.1–61.7 °C) Ir[34,35] and ^{1}H NMR[34] spectra agreed with the literature. GLC analysis on an 0.125 in. × 4 ft 20% Apiezon L on 60/80 Chromosorb W column at 200 °C showed this material to contain <0.5% of *anti*-Br.

Exclusion of Water and Oxygen from Grignard Reactions. All preparations were run under dry nitrogen at slightly above atmospheric pressure. All deuterolyses were performed under nitrogen at room temperature (23–25 °C). All solvents, solutions, and liquid reagents were transferred by syringes which were dried at 160 °C and stored in a desiccator. Grignard reactions were performed in 14/20 standard taper glassware that consisted of a three-neck round-bottom flask, magnetic stirring bar, condenser, addition funnel, and rubber septum. All but the septum were dried at 160 °C overnight and then flame dried under a dry nitrogen flow. The alkyl halides were vacuum dried and weighed into oven-dried vials. They were dissolved in THF under nitrogen and transferred to the addition funnel by syringe.

Typical Procedure for Grignard Preparations with Magnesium Turnings (Expt 16–18). To 0.55 g (22.6 mg-atoms) of magnesium turnings under 5 ml of THF, 0.212 g (1.13 mmol) of 1,2-dibromoethane was added dropwise at a rate which maintained reflux. Another 7 ml of THF was added, the mixture was refluxed for 1–2 h, and 0.250 g (1.13 mmol) of *anti*-Br in 3 ml of THF was added dropwise in 2–5 min at reflux. After the additional heating time indicated in Table I the mixture was cooled to room temperature, 5 ml of D_2O was added, and the mixture was stirred for at least 15 min.

This procedure was used on scales of 0.25–2.25 g of **1c**, 0.10 g of **1a** and **1b**, and 0.60 g of **1d**. Progress of the reaction was followed by quenching a 5–10-μl aliquot of the reaction mixture in saturated NH_4Cl (aqueous) and analyzing an ether extract by GLC. Naphthalene (ca. 100 mg) was added to the deuterolyzed mixture as an internal standard for the GLC analysis, and the excess Mg was destroyed with 3 ml of saturated NH_4Cl (aqueous). The phases were separated, and the aqueous phase was extracted with several portions of ether. The combined ethereal extracts were washed with saturated NaCl (aqueous), dried ($MgSO_4$), and concentrated to about 2 ml. Yield was determined by GLC analysis of the concentrate, and **2** was isolated by preparative GLC. By the method of Cristol and Noreen,[16] a 10% molar excess of 1,3-diphenylisobenzofuran was added to **2** and heated in a sealed tube at 120 °C for 20 h. The adduct (**6**) was recrystallized one or two times from ethanol/chloroform, vacuum dried, and analyzed for deuterium content.

Typical Procedure for Grignard Preparations from Activated Magnesium (Expt 21–24). This procedure is based on the method of Rieke and co-workers.[14] A solution of 0.565 g (3.00 mmol) of 1,2-dibromoethane in 5 ml of THF was added dropwise with stirring to 153.6 mg (6.3 mg-atoms) of magnesium turnings in 10 ml of THF at a rate which maintained reflux, and the mixture was refluxed for another 1–2 h. Freshly cut potassium metal (217 mg, 5.54 mg-atoms) was added, and the mixture was refluxed for 2 h to produce a gray suspension of activated magnesium. After cooling to room temperature, 0.50 g (2.26 mmol) of *anti*-Br in 5 ml of THF was added and the progress of the reaction was checked by GLC. The reaction was usually complete in 3–7 h. In expt 22, naphthalene was added as an internal GLC standard, and half of the reaction mixture was removed by syringe and quenched in D_2O. The remaining half was refluxed for 4 h, cooled to room temperature, and quenched with D_2O. Products from each half of the reaction were isolated independently in the manner described for mgnesium turning experiments. Experiments 23 and 24 were done similarly, except that the naphthalene was added to each aliquot after removal and quench.

Typical Procedure for Grignard Preparation from Magnesium Halide and Sodium Naphthalenide (Expt 4, 5, 14, 15, 26). A. Standard Magnesium Halide Solutions. A solution of 1.5 g (15 mmol) of 1,2-dichloroethane in 10 ml of THF was added dropwise with stirring to 730 mg (30.0 mg-atoms) of magnesium turnings in 10 ml of THF at a rate which maintained reflux. Another 30 ml of THF was added, and the mixture was filtered under nitrogen through a course porosity sintered glass frit into a dry flask. Typical quantities used in preparing the analogous $MgBr_2$/THF solutions were 4.51 g (24.0 mmol) of 1,2-dibromoethane, 1.22 g (50.0 mg-atoms) of Mg, and a total of 80 ml of THF. This resulted in a saturated $MgBr_2$/THF solution as indicated by a white, crystalline precipitate. Molarities of these solutions (typically 0.30 M $MgCl_2$ and 0.23 M $MgBr_2$) were determined by both EDTA titration of Mg^{2+} and Ag^+ titration for X^-, which indicated that the reactions were quantitative.

B. Sodium Naphthalenide (NaNaph) Solutions. A large excess of sodium metal was added to 3.84 g (30.0 mmol) of naphthalene in 30 ml of THF. The solution turned green within seconds after the addition of the sodium and was stirred for 2–10 h. The green solution was separated from the excess sodium and transferred to a dry flask under nitrogen by syringe. The solution was analyzed by quenching an aliquot in ethanol and titrating with standard HCl (aqueous) solution to the bromcresol green end point.[36] NaNaph was usually 0.7–0.9 M. Only fresh solutions of NaNaph worked satisfactorily. Solutions aged for 1 week or more still showed the same total base concentration, but failed to consume all the starting halide in the Grignard preparations.

C. Grignard Preparations. By the method of Bank and Bank,[15] 1.3 mmol of NaNaph from a standardized solution was added dropwise with stirring at room temperature to a solution prepared from 100.0 mg (0.57 mmol) of *anti*-Cl in 0.4 ml of THF and 0.75 mmol of standardized $MgCl_2$ solution. In the case of *anti*-Br 250 mg (1.13 mmol) of *anti*-Br, 1.7 mmol of $MgBr_2$, and 2.67 mmol of NaNaph were used. The solution was stirred for about 15 min after the addition was complete, quenched with D_2O, and stirred for at least 15 min. The product **2** was isolated in the usual manner using ca. 150 or 250 mg of n-$C_{14}H_{30}$ as the internal GLC standard rather than naphthalene.

Procedural Variations in Specific Experiments. In Table I, 65 °C refers to refluxing THF and 25 °C means room temperature. Times refer to time after addition of the alkyl halide was complete. In experiments with more than one data point a single reaction mixture was prepared and aliquots were withdrawn by syringe at the times indicated. The reaction mixture was chilled briefly in an ice bath before sample withdrawal, and heating was resumed immediately afterward. In reactions of chlorides **1a** and **1b**, 1,2-dichloroethane, rather than 1,2-dibromoethane, was used to precondition the magnesium turnings or to generate the $MgCl_2$ from which activated magnesium was prepared.

Expt 3. 7-Oxabicyclo[2.2.1]heptane was used as solvent in place of THF.

Expt 6. The $MgCl_2$ was omitted from the NaNaph procedure.

Expt 7. A Grignard solution was prepared from *anti*-Cl and Mg turnings by the standard procedure and cooled to room temperature. Standard NaNaph solution (2.5 equiv) was added, the mixture was stirred for 15 min, and deuterolysis was carried out by the standard procedure. .

Expt 8, 9. After the standard $MgCl_2$/NaNaph treatment the reaction mixture was refluxed for 24 h before deuterolysis.

Expt 25. Turnings from Dow singly sublimed magnesium crystal rather than reagent grade magnesium turnings were used.

Expt 30, 32. THF-d_8 (see Materials section) rather than THF was used and H_2O rather than D_2O was used for hydrolysis.

Expt 31. The solvent was THF-d_8. An aliquot was removed after 30 min at reflux and hydrolyzed with D_2O. The remaining solution was refluxed for 240 h and hydrolyzed with H_2O.

Benzonorbornadiene Dimer 9 (Expt 21). The usual activated magnesium with 1.00 g (4.52 mmol) of *anti*-Br was used. No naphthalene was added. After the usual extractions the solvent was removed under vacuum and replaced with hexane. The hexane solution was chromatographed on 100 g of silica gel taking 25-ml fractions. Fractions 1–80 were eluted with hexane, 81–150 with 1% ether in hexane, 151–200 with 2% ether in hexane, 201–250 with 5% ether in hexane, and 251–300 with 10% ether in hexane. Fractions 1–30 contained **2** and were combined and concentrated to a solution weighing 0.6728 g. By GLC analysis, the area of **2** compared to the total area of **2** and the solvent peak was 78%, which corresponds to a yield of 525 mg (82%). This solution was treated with 1.0 g (3.7 mmol) of 1,3-diphenylisobenzofuran and adduct **6** was purified in the usual manner.

Fractions 40–80 were combined and evaporated to dryness to yield 36.5 mg (0.130 mmol, 5.7%) of dimer **9**: ^{1}H NMR (CCl_4) δ 2.00 (broad d, 1 H, J = 10 Hz), 2.78 (broad d, 1 H, J = 10 Hz), 3.32–3.64 (broad m, 4 H), 6.42–6.60 (m, 4 H), 6.60–7.16 (m, 8 H); ir (KBr) 1448 (m), 1300 (m), 1285 (m), 757 (s), 727 (s), 682 (s), and 632 cm^{-1} (m); mass spectrum (70 eV) *m/e* (rel intensity) 284 (0.81), 283 (4.05), 282 (16.38), 281 (5.24), 167 (15.83), 155 (5.85), 154 (36.46), 153 (28.72), 142 (13.62), 141

(100.00), 128 (26.15), 115 (20.82). Other column fractions yielded no identifiable products.

Hexamethylphosphoramide Treatment and Carbonation of Grignard Reagent from *anti*-Br (Expt 20). The Grignard reagent was prepared from 2.25 g (10.2 mmol) of *anti*-Br and magnesium turnings in 70 ml of THF. A 7-ml aliquot was removed and quenched in D_2O, and a 20-ml aliquot was removed and injected into a flask of freshly powdered dry ice. As quickly as possible, 8 ml (45.7 mmol) of HMPA was added to the remaining Grignard solution. An 8.3-ml aliquot was removed and quenched in D_2O, a 23.7-ml aliquot was removed and quenched in dry ice, and 1.0 g (9.3 mmol) of chlorotrimethylsilane was added to the remaining 19 ml of solution. The deuterolyzed mixtures were purified in the usual manner. The chlorotrimethylsilane mixture was stirred overnight, saturated NH_4Cl solution was added to destroy excess magnesium, the phases were separated, the aqueous phase was extracted with ether, and the ether extracts were dried ($MgSO_4$). Analysis by GLC showed four peaks in the volatility range expected for 7-trimethylsilylbenzonorbornadienes, so no further isolation was attempted.

After warming to room temperature, water was added to the mixture carbonated without HMPA and it was acidified with concentrated HCl. The aqueous phase was extracted with several portions of ether, and the combined ether phases were extracted with three 50-ml portions of 1 N NaOH. The combined NaOH extracts were washed with ether, acidified, and extracted with ether. The ether was evaporated and the resultant solid was vacuum dried to yield 56.0 mg (0.301 mmol, 10.3%) of 7-benzonorbornadienecarboxylic acids. The acids were esterified by refluxing overnight in 5 ml of methanol with 0.1 ml of concentrated H_2SO_4. Addition of water followed by ether extraction and evaporation gave 46.6 mg (0.233 mmol, 78%) of 7-carbomethoxybenzonorbornadienes (7 and 8). The aliquot that was carbonated after addition of HMPA was treated in an analogous manner to give 35.0 mg (0.188 mmol, 6.5%) of 7-benzonorbornadienecarboxylic acids and 24.1 mg (0.121 mmol; 64.5%) of 7 and 8. GLC analyses of these samples on a 0.125 in. × 4 ft 10% FFAP on 60/80 Chromosorb G column at 200 °C showed anti/syn ratios of esters of 6.8 and 3.0, respectively, for the carbonations with and without HMPA. The structures of 7 and 8 were confirmed by comparison of their GLC properties and NMR spectra with those of known samples (vide infra).

Deuterium Analyses. Mass spectra of adduct 6 were run at ca. 8.5 eV to minimize fragmentation. The data were processed as follows. Let P_0 = peak height of parent peak of 6 at *m/e* 412 and P_1 = peak height of peak at *m/e* 413. The experimentally measured natural abundance P_1/P_0 ratio was 0.3485 (theory, 0.3348). Thus atom excess $D = [P_1 - (0.3485)(P_0)]/[P_1 - (0.3485)(P_0) + P_0]$. Duplicate analyses of three different samples gave values which never differed by more than 0.008 atom excess D.

^1H NMR spectra of 6 in $CDCl_3$ were obtained on a Varian HA-100 spectrometer using either Me_4Si or CH_2Cl_2 for the lock signal. The spectra were integrated five times and the deuterium incorporation was determined from the sum of the five integrals for each adsorption as follows. Let H_a = the area for protons H_a (δ 2.45) in 6, H_b = the area for protons H_b (δ 3.04), H_c = the area for proton H_c (δ 1.27), and H_d = the area for proton H_d (δ 2.88). Three spectra of two independently prepared all-protio samples of 6 were run. Using a Me_4Si lock H_c and H_d integrated on the average to 1.05 ± 0.05 protons when the total areas for H_a and H_b divided by 4 was considered equal to the area per proton. Using this correction factor

$$\text{atom excess D syn} = 1 - \left[\frac{H_c}{(H_a + H_b)/4}\right]\left[\frac{1}{1.05}\right]$$

$$\text{atom excess D anti} = 1 - \left[\frac{H_d}{(H_a + H_b)/4}\right]\left[\frac{1}{1.05}\right]$$

With a CH_2Cl_2 lock, the corresponding correction factors were 1.01 for the syn position and 1.04 for the anti position. Occasionally ^1H NMR analyses gave total deuterium content which differed from the mass spectral analysis by >0.10 atom excess D. In such cases the ^1H NMR analyses were repeated and closer agreement with mass spectrometry was found. However, we do not claim that the ^1H NMR analyses are any better than ±0.05 atom excess D at each position.

***anti*-7-Carbomethoxybenzonorbornadiene (7).** At −78 °C 1.82 ml of 1.9 M *sec*-butyllithium (Alfa) was added to a solution of 601.5 mg (2.73 mmol) of *anti*-Br in 24 ml of dry ether. The solution was allowed to warm to 0 °C, was cooled back to −78 °C, and was added by syringe to freshly crushed dry ice. After the carbonated mixture had warmed to room temperature, the phases were separated, and the aqueous phase was extracted with several portions of ether. The combined ethereal extracts were extracted with two 60-ml portions of 1 N NaOH. The NaOH extracts were washed with ether and acidified with HCl. The precipitated carboxylic acid (200 mg) was filtered, vacuum dried, and esterified by refluxing in 10 ml of methanol with 0.25 ml of concentrated H_2SO_4 for 23 h. After the addition of 40 ml of ice water, the solution was extracted with several portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with saturated NaCl, dried ($MgSO_4$), and evaporated to 216.7 mg of dry solid. Preparative GLC on a 0.25 in. × 10 ft 20% SE-30 on 60/80 Chromosorb W column at 210 °C gave 95.9 mg (0.48 mmol, 17.6%) of 7. Only one minor component (1.2%) of comparable retention time could be seen by preparative GLC, but it was not isolated. No impurities or other isomers could be detected in the purified product by GLC analysis on a 0.125 in. × 4 ft 10% FFAP on 60/80 Chromosorb G column at 200 °C: ir (KBr) 3020 (m), 1733 (s), 1455 (m), 1440 (m), 1350 (m), 1295 (m), 1247 (s), 1220 (s), 1180 (m), 1170 (m), 1020 (m), 1012 (m), 918 (m), 772 (s), 743 (s), and 709 cm^{-1} (s); mass spectrum (70 eV) *m/e* (rel intensity) 202 (0.21), 201 (3.18), 200 (23.51), 185 (5.12), 169 (13.34), 168 (71.40), 157 (6.04), 142 (13.38), 141 (100.00), 129 (19.71), 116 (6.46), 115 (51.69); ^1H NMR (CCl_4) δ 3.17 (t of t, 1 H, J = 1.75, 0.35 Hz), 3.53 (s, 3 H), 4.08 (q, 2 H, J = 1.83 Hz), 6.61 (t of d, 2 H, J = 1.95, 0.35 Hz), 6.96 (AA'BB', 4 H); irradiation at δ 6.61 converts the δ 3.17 absorption to a simple triplet, J = 1.75 Hz, confirming the anti configuration.

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.01; H, 5.94.

Equilibration of *anti*- and *syn*-7-Carbomethoxybenzonorbornadienes (7 and 8). A mixture of 70.6 mg (0.40 mmol) of 7, 0.20 ml of HMPA, and 0.8 ml of 0.53 M sodium methoxide in methanol was heated at 65 °C. Aliquots of 3–5 μl were removed and analyzed by GLC on a 0.125 in. × 4 ft 10% FFAP on 60/80 Chromosorb G column at 200 °C. After 165 h equilibrium was attained since there was no further change in the ratio of anti to syn esters up to 333 h, $K_{eq} = [8]/[7] = 0.73$. Least-squares analysis of the composition vs. time data plotted as a first-order rate process gave a straight line with slope = 3.415×10^{-4} $min^{-1} = k_f + k_r$, the sum of the forward and reverse rate constants. Thus $k_f = 1.44 \times 10^{-4}$ min^{-1} and $k_r = 1.97 \times 10^{-4}$ min^{-1}. ^1H NMR (CCl_4) of the equilibrium mixture showed both 7 (vide supra) and 8: δ 3.26 (t, 1 H, J = 1.75 Hz), 3.33 (s, 3 H), 4.01 (q, 2 H, J = 1.92 Hz), 6.70 (t, 2 H, J = 2 Hz), 6.8–7.2 (AA'BB').

Grignard Reagent from *anti*-7-Bromobenzonorbornene (5). The general procedure with magnesium turnings was used with 1.00 g (4.48 mmol) of 5 and a reaction time of 5 min at reflux. The reaction mixture was hydrolyzed with 40 ml of D_2O, and the resultant benzonorbornene (79% by GLC) was isolated by preparative GLC under identical conditions with isolation of 2. Deuterium analyses were carried out by mass spectrometry and by 220-MHz ^1H NMR using methods analogous to those described for 2.

Registry No.—1a, 10239-89-1; 1b, 14518-75-3; 1c, 7605-10-9; 1d, 22436-26-6; 2, 4453-90-1; 2 (7-*d*), 31893-09-1; 5, 7605-11-0; 6, 58475-66-8; 7, 58475-67-9; 8, 58525-37-4; 9, 14518-80-0; *anti*-7-benzonorbornadienol, 6991-42-0; magnesium, 7439-95-4; 1,2-dibromoethane, 106-93-4; sodium naphthalenide, 3481-12-7; 1,2-dichloroethane, 107-06-2; $MgCl_2$, 7786-30-3; $MgBr_2$, 7789-48-2; hexamethylphosphoramide, 680-31-9.

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Effects of a Remote Double Bond or Cyclopropane Ring on Electrophilic Aromatic Substitution[1]

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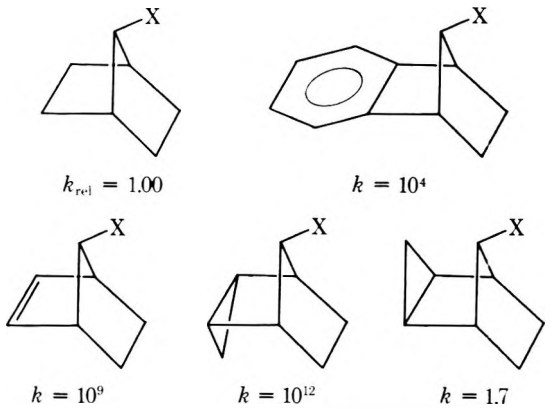
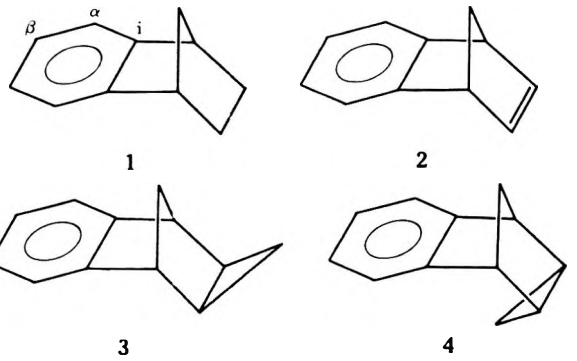
Relative positional reactivities have been determined for nitration of benzonorbornene (1), benzonorbornadiene (2), and the corresponding *exo*- and *endo*-benzotricyclo[3.2.1.$0^{2,4}$]octenes (3 and 4). For β positions, homoconjugation in 2 and 3 dominates over hyperconjugative effects; for α and ipso positions, inductive effects dominate. A "buttressed fused ortho effect" is proposed to account for the lower α reactivity of 3 than of 4.

There is continued widespread interest in interactions between electron-deficient centers and remote (i.e., nonconjugated) double bonds, arenes, and cyclopropane rings.[2] However, little attention has been turned to the effects of a remote double bond or cyclopropane ring on electrophilic substitution reactions of an aromatic ring; experimental approaches to determination of optimum geometries for such interactions have not been reported. Consideration of the literature on remote participation effects facilitated a choice of substrates for this type of study. As summarized recently,[2a] conformationally mobile molecules thus far have afforded no kinetic evidence of significant contributions from cyclopropane participation. In contrast, fusion of a cyclopropane ring into a rigid framework has produced some of the most dramatic solvolysis rate variations known, as exemplified by the group of compounds formulated below (X = brosylate or *p*-nitrobenzoate).[3]



It was anticipated, therefore, that kinetically detectable interaction between arene and remote cyclopropane (or double bond) moieties would be found in a study of the series of rigid structures 1–4. Further impetus was given to this work by the discovery[4] that 1 undergoes detectable (~3%) ipso[5] (i) nitration; thus the influence of remote substituents might be accessible via measured reactivities at each of three distinct arene positions.



Results and Discussion

Benzonorbornadiene (2), prepared by established methods,[6] was converted to 1 by catalytic hydrogenation and to a 95:5 mixture of 3 and 4 by Simmons–Smith cyclopropanation.[7,8] Pure 3 was obtained by crystallization from the mixture; pure 4 was obtained by chromatography of the enriched mother liquor.

Certain features of the nitration study by Tanida and Muneyuki[9] were adapted to the present work; indan and tetralin were nitrated for comparison purposes, with the latter used as a standard (rel rate = 1.00) for computation of substrate reactivities. Because of the sensitivity of **2**, **3**, and **4** toward other nitrating agents, nitrations were performed with copper nitrate in acetic anhydride (0 °C). Product mixtures were subjected to VPC analysis; product distributions were checked against artificial mixtures of similar composition. Percentages of nitro compounds (α and β) for **1**, indan, and tetralin were nearly identical with those previously re-

Table I. Isomer Ratios and Relative Rates for Nitration of 1. Indan, and Tetralin in Different Media

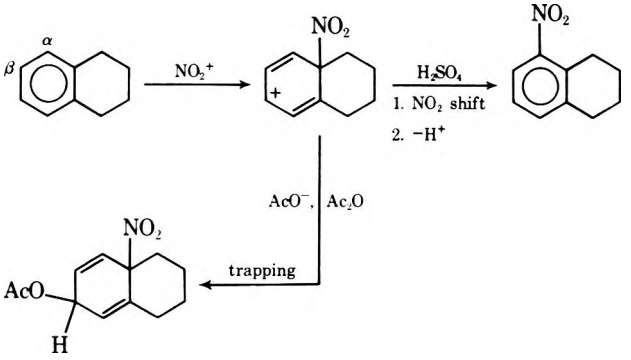
Substrate	α:β Ratio[c]	Rel rate
1[a]	7/93	1.88
1[b]	3/97	3.92
Indan[a]	50/50	1.27
Indan[b]	27/73	1.01
Tetralin[a]	52/48	1.00[d]
Tetralin[b]	37/63	1.00[d]

[a] Reference 9; HNO_3–H_2SO_4, CH_3NO_2, 0 °C. [b] This work; $Cu(NO_3)_2 \cdot 3H_2O$, Ac_2O, 0 °C. [c] In the present work, duplicate nitrations were done for each substrate; distributions were within ± 3% of the average values. Repetitions of work done elsewhere gave equally good agreement. [d] Standard of comparison.

ported[9,10] for nitration in nitric acid–acetic anhydride. To interrelate nitration rates, pairwise competitive nitrations were performed: 1 vs. 2, 3, indan, and tetralin; 3 vs. 4; 4 vs. indan; indan vs. tetralin. Percentages of both isomers of both compounds in each competition were determined and checked as in individual nitrations.

Discussion will center first on those aspects of the present results bearing on attack of the nitrating agent at ipso positions. Tanida and Muneyuki,[9] on nitrating 1, indan, and tetralin with nitric–sulfuric acid, reported 1 to be about twice as reactive as the other two substrates (Table I). However, nitric–sulfuric acid nitration now is known to allow ipso nitroarenium ions (exemplified by tetralin in Scheme I) to

Scheme I



rearrange and deprotonate, falsely enhancing the reactivity of the α position. Nitration in acetic anhydride leads to extensive[11] trapping of these nitroarenium ions (Scheme I); α-nitro derivative then is *not* the ultimate product of normal workup. Because indan and tetralin appear to undergo ca. 50% ipso attack[10,12] whereas 1 gives evidence of only 3% ipso attack,[4] the α reactivities for indan and tetralin, as well as the total substrate reactivities toward *direct* (non-ipso) nitration are inflated in the Tanida–Muneyuki work, relative to the corresponding values for 1. When the ipso effect is taken into account, closer agreement is found between the two studies, although our nitration conditions still appear to afford a more selective nitrating agent.

Results of nitration of all substrates in the present study are assembled in Table II. Because no ipso nitration was observed for 2, 3, or 4, ipso partial rate factors have been omitted for all compounds,[13] and the relative rates given are only for non-ipso aromatic nitration. That they are reliable in this regard is indicated by the stability of all nitro derivatives under conditions of nitration and workup.[14]

With a few exceptions, the range of relative rates is not large. Interpretation therefore is confined here to salient features, with more extensive discussion available as supplementary material (see paragraph at end of paper).

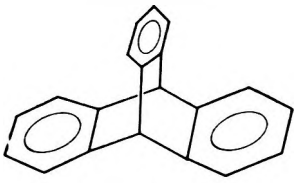
The inertness of ipso and α positions in 2–4 (at least 50

Table II. Relative Rates[a] and Partial Rate Factors[b] for Nitration[c] of Selected Benzomono-, -bi-, and -tricyclic Compounds

Compd	Structure	Rate[c]	α/β[d]	α_f	β_f
3		6.47	0.2/99.8	0.02	10.2
2		6.28	0.1/99.9[e]	0.01[e]	9.9
1		3.92	2.9/97.1	0.18	6.0
Tetralin		1.00	37/63	0.56	1.00
Indan		1.01	27/73	0.43	1.2
4		0.84	5.8/94.2	0.08	1.2

[a] Relative to tetralin. [b] Relative to the β position of tetralin. [c] Competitive nitration with copper nitrate in acetic anhydride at 0 °C. [d] See footnote c, Table I. [e] Approximate value.

times less reactive than the β positions in 2 and 3) is attributed principally to inductive electron withdrawal from these positions. These results are consistent with previous reports of very high preferences for β-nitration in triptycene (5),[15] janusene (6),[16] and other compounds containing homoconjugated



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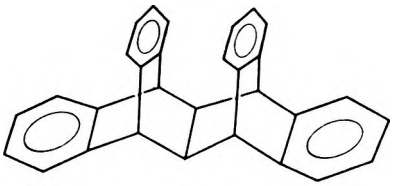

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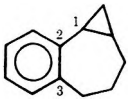
π systems.[15] Precedent for inductive deactivation of an ipso position by a cyclopropyl group is found in the apparently complete preference for ipso attack at C_3 in substrate 7.[17,18]



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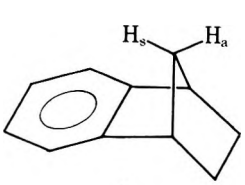
An a priori unexpected feature of Table II is the greater α reactivity of 4 than of 3. No α-activating effect can be proposed for 4, relative to 3; we suggest a deactivating steric factor for 3. The C_7 syn proton (H_s) in 1 has been held responsible for some of the steric hindrance to α-attack in 1 ("fused ortho effect").[9] Incorporation of an exo (but not an endo) cyclopropane ring into that skeleton (to give 3) introduces severe nonbonding interaction between H_a and a cyclopropane methylene hydrogen. This interaction should force the methylene bridge (H_s) closer to the α carbons, generating a "buttressed fused ortho effect" in this case. The viability of



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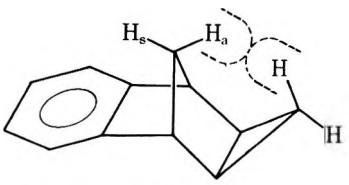


3

this explanation is under study.

Experimental Section

Proton magnetic resonance spectra were obtained with a Varian A-60 or a Varian XL-100; ultraviolet spectra were recorded on a Perkin-Elmer Model 202 or a Cary 118. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Melting and boiling points are uncorrected.

***exo*- and *endo*-Benzo[6,7]tricyclo[3.2.1.0^{2,4}]octane (3 and 4).** These compounds were prepared as a 95:5 mixture from benzonorbornadiene using the Simmons–Smith procedure.[7] Separation of the isomers began with low-temperature crystallization of **3** from pentane until **4** had been enriched to 20–30%. Pure **4** then was obtained by chromatography on silica gel, using pentane as the elutant. Physical properties of **3** and **4** are given below.

3: mp 37 °C (lit.[20] 35–37 °C); bp 40–41 °C (1 mm); ir (neat, NaCl) 3000 (cyclopropyl C–H), 1485, 1438, 1290, 1258, 1240, 1160, 1140, 1085, 1065, 970, 940, 930, 897, 860, 820, 799, 735, 720, and 677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.1 (m, 4 H, aryl), 3.27 (s, 2 H, H_1 and H_5), and 1.65–0.68 (m, 6 H, $-CH_2-$ and cyclopropyl H's).

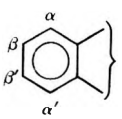
4: bp 38–39 °C (1 mm); ir (neat, NaCl) 2950 (cyclopropyl C–H), 1380, 1150, 1115, 980, 780, 740, 710, and 678 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.05 (s, 4 H, aryl), 3.27 (m, 2 H, bridgehead H's), 2.25 (dt, 1 H, J = 2.0, 8.0 Hz, syn H_8), 2.0 (d, 1 H, J = 8.0 Hz, anti H_8), 1.63 (m, 2 H, H_2 and H_4), 0.45 (m, 1 H, anti H_3), and −0.70 (overlapping dt, 1 H, J = 2.0, 6.0 Hz, syn H_3).

Indan was prepared from distilled indene by hydrogenation over 10% Pd/C in a Parr hydrogenator. Commercial tetralin was passed through a column of alumina and distilled prior to use, as was indan.

General Procedure for Nitration with Copper Nitrate Trihydrate. The hydrocarbon in acetic anhydride was pipetted into a cooled (0 °C in an ice–salt bath) round-bottom flask. Freshly powdered copper nitrate trihydrate was added to the cooled solution, and the reaction was maintained at 0 °C with magnetic stirring for 1–2 h. The mixture was poured onto ice and an equal volume of water was added. Solid sodium bicarbonate was added to the magnetically stirred solution at 0 °C. When no more gas evolution (CO_2) was observed, the water layer was extracted three times with half volumes of ether. The combined ether layers were washed once with an equal volume of 5% aqueous sodium bicarbonate and once with an equal volume of water. The solution was dried ($MgSO_4$) and ether was removed on a rotary evaporator. The nitro compounds were isolated by column chromatography on silica gel (60–80 mesh, grade 95%, Fisher S-662, 30:1) using pentane to elute starting material and benzene–pentane (20:80 → 50:50; depending on the compounds) to elute the nitro compounds.

Nitro derivatives of **2**, **3**, indan, and tetralin were separated as described above. Nitro derivatives of **1** and **4** were separated using high-pressure liquid chromatography on Porasil columns.

The physical properties and spectral data of the nitro derivatives of **1**–**4** are given below, using the nomenclature shown on the partial formula.



α-NO_2-1: bp 140–141 °C (6 mm);[9] ir (neat, NaCl) 1520 and 1340 cm^{-1} ($-NO_2$); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1 H, J = 8.0 Hz, β-H), 7.45 (d, 1 H, J = 8.0 Hz, α'-H), 7.2 (t, 1 H, J = 8.0 Hz, β'-H), 4.25 (m, 1 H, benzyl H near NO_2), 3.45 (m, 1 H, other benzyl H), 2.2–1.5 [m, 4 H, $-(CH_2)_2-$], and 1.1 (broad s, 2 H, $-CH_2-$); uv λ_{max} (hexane) 275 nm (ϵ 5180) and 302 (1500).

β-NO_2-1: bp 140–142 °C (6 mm);[9] ir (neat, NaCl) 1520 and 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 1 H, J = 2.0 Hz, α-H), 8.07 (dd, 1 H, J = 2.0, 8.0 Hz, β'-H), 7.42 (d, 1 H, J = 8.0 Hz, α'-H), 3.50 (broad s, 2 H, bridgehead H's), 2.22–1.50 [m, 4 H, $-(CH_2)_2$], and 1.18 (m, 2 H, $-CH_2-$); uv λ_{max} (hexane) 271 nm (ϵ 8460).

α-NO_2-2: this isomer was not positively identified; a small VPC peak of suitable retention time was seen in the mother liquor from crystallization of the β isomer; the α isomer must constitute less than 0.1% of the product mixture.

β-NO_2-2:[21] mp 38–38.5 °C; ir (KBr) 1520 and 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1 H, J = 2.0 Hz, α-H), 7.85 (dd, 1 H, J = 2.0, 8.0 Hz, β'-H), 7.28 (d, 1 H, J = 8.0 Hz, α'-H), 6.80 (broad s, 2 H, vinyl H's), 3.95 (m, 2 H, bridgehead H's), and 2.33 (m, 2 H, $-CH_2-$); uv λ_{max} (hexane) 280.5 nm (ϵ 6625); uv λ_{max} (EtOH) 290 nm (ϵ 7900).

α-NO_2-3: ir (KBr) 1520 and 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78 (dd, 1 H, J = 2.0, 8.0 Hz, β-H), 7.36 (dd, J = 2.0, 8.0 Hz, α'-H), 7.12 (t, 1 H, J = 8.0 Hz, β'-H), 4.20 (broad s, 1 H, benzyl H near NO_2), 3.40 (broad s, 1 H, other benzyl H), and 1.74–0.68 (m, 6 H, $-CH_2-$ bridge and cyclopropyl H's); uv λ_{max} (hexane) 259 nm (ϵ 7500); MS *m/e* 201 ($M\cdot^+$, 12.5%).

β-NO_2-3: mp 79–80 °C; ir (KBr) 1520 and 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 1 H, J = 2.0 Hz α-H), 8.01 (dd, 1 H, J = 2.0, 8.0 Hz, β'-H), 7.35 (d, 1 H, J = 8.0 Hz, α'-H), 3.40 (s, 2 H, H_1 and H_5), and 1.72–0.63 (m, 6 H, $-CH_2-$ bridge and cyclopropyl H's); uv λ_{max} (hexane) 276 nm (ϵ 9050); uv λ_{max} (EtOH) 290 nm; MS *m/e* 201 ($M\cdot^+$, 40.5%).

α-NO_2-4: ir (neat, NaCl) 1520 and 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88 (dd, 1 H, J = 2.0, 8.0 Hz, β-H), 7.35 (dd, 1 H, J = 2.0, 8.0 Hz, α'-H), 7.26 (t, 1 H, J = 8.0 Hz, β'-H), 4.29 (m, 1 H, benzyl H near NO_2), 3.43 (m, 1 H, other benzyl), 3.34 (td, 1 H, J = 2.0, 8.0 Hz, syn H_8), 2.08 (broad d, 1 H, J = 8.0 Hz, anti H_8), 2.00–1.72 (m, 2 H, H_2 and H_4), 0.57 (dt, 1 H, J = 3.0, 6.0 Hz, anti H_3), and −0.74 (td, 1 H, J = 3.0, 6.0 Hz, syn H_3); uv λ_{max} (hexane) 260 nm (ϵ 3000); MS *m/e* 201 ($M\cdot^+$, 15%).

β-NO_2-4: ir (neat, NaCl) 1520 and 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (dd, 1 H, J = 2.0, 8.0 Hz, β'-H), 7.91 (d, 1 H, J = 2.0 Hz, α-H), 7.32 (d, 1 H, J = 8.0 Hz, α'-H), 3.43 (broad s, 2 H, H_1 and H_5), 3.34 (td, 1 H, J = 2.0, 8.0 Hz, syn-H_8, 2.08 (broad d, 1 H, J = 8.0 Hz, anti H_8), 1.93 (m, 2 H, H_2 and H_4), 0.57 (m, 1 H, anti H_3), and −0.70 (td, 1 H, J = 3.0, 6.0 Hz, syn H_3); uv λ_{max} (hexane) 272.5 nm (ϵ 8370); MS *m/e* 201 ($M\cdot^+$, 100%).

The spectral data and physical constants of the nitro isomers of indan and tetralin were identical with those reported in the literature.[12b]

General Procedure for Competitive Nitrations. The distribution of nitro compounds from competitive nitrations was obtained using VPC analysis (10% QF-1 on 60–80 Chromosorb W, 5 ft × 0.125 in. column at 150–220 °C, Aerograph Hy-Fi Model 600-C).

The nitration conditions were identical with those described above. A typical competition was run as follows. The two competing arenes (7.6 mmol each) were dissolved in 10–20 ml of acetic anhydride. To this solution at 0 °C was added 3.8 mmol of freshly powdered copper nitrate trihydrate. The reaction was allowed to proceed for 1–2 h and worked up as for preparative nitrations, except that all nitro compounds were taken off the silica gel column together and weighed. VPC analyses were checked by comparing the results with artificial mixtures of similar composition. Relative reactivities were calculated from the expression derived by Ingold and Shaw.[22]

Registry No.—**1**, 4486-29-7; **α-NO_2-1**, 4228-29-9; **β-NO_2-1**, 4228-30-2; **2**, 4453-90-1; **α-NO_2-2**, 58673-43-1; **β-NO_2-2**, 42810-33-3; **3**, 15577-76-1; **α-NO_2-3**, 58673-44-2; **β-NO_2-3**, 58673-45-3; **4**, 58717-04-7; **α-NO_2-4**, 58717-05-8; **β-NO_2-4**, 58717-06-9; tetralin, 119-64-2; indan, 496-11-7.

Supplementary Material Available. A more extensive discussion of partial rate factors and appropriate external comparisons (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Preliminary report: M. W. Galley and R. C. Hahn, Abstracts, 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 8–13, 1974, No. ORGN-38.
(2) (a) J. Haywood-Farmer, *Chem. Rev.*, **74**, 315 (1974), and references cited therein; (b) G. R. Wenzinger and J. A. Ors, *J. Org. Chem.*, **39**, 2060 (1974); (c) P. E. Schueler and Y. E. Rhodes, *ibid.*, **39**, 2063 (1974); (d) G. Ellen and G. W. Klumpp, *Tetrahedron Lett.*, 3637 (1974).
(3) Values are approximate; see Table X, ref 2a, for data sources, experimental conditions, extrapolations, and related compounds.
(4) M. W. Galley and R. C. Hahn, *J. Am. Chem. Soc.*, **96**, 4337 (1974).
(5) C. L. Perrin and G. A. Skinner, *J. Am. Chem. Soc.*, **93**, 3389 (1971).
(6) (a) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958); (b) H. Tanida, T. Tsuji, and H. Ishitobi, *J. Am. Chem. Soc.*, **86**, 4904 (1964).
(7) R. D. Smith and H. E. Simmons, *Org. Synth.*, **41**, 72 (1961).
(8) Professor M. A. Battiste (private communication) also has noted formation of small amounts of **4** on reaction of **2** with diazomethane.
(9) H. Tanida and R. Muneyuki, *J. Am. Chem. Soc.*, **87**, 4794 (1965).
(10) J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron*, 21, 1665 (1965).
(11) Ipso attack percentages cited here must be regarded as minimum values; even in "trapping" media, nitroarenium ions may be partitioned between

trapping and nitro migration. However, data available so far are consistent with the assumption of essentially complete trapping.

(12) (a) A. Fischer, C. C. Greig, A. L. Wilkinson, and D. R. A. Leonard, *Can. J. Chem.*, **50**, 2211 (1972); (b) A. Fischer and D. R. A. Leonard, *ibid.*, **50**, 3367 (1972).

(13) Ipso partial rate factors in benzo-fused bi- and tricyclic systems currently are under separate study, and will be reported in due course.

(14) Nitrations of **2–4** with copper nitrate–acetic anhydride are not clean; benzonorbornadiene, in particular, gives considerable amounts of products derivable at least in part from reaction of the isolated double bond. Introduction of the nitro group, however, appears to stabilize nitro derivatives toward further electrophilic attack. Side reactions of **2–4** do not affect the data presented.

(15) B. H. Klanderman and W. C. Perkins, J. Org. Chem., **34**, 630 (1969), and references cited therein.

(16) S. J. Cristol and D. C. Lewis, *J. Am. Chem. Soc.*, **89**, 1476 (1967).

(17) R. C. Hahn and M. B. Groen, *J. Am. Chem. Soc.*, **95**, 6128 (1973).

(18) A referee has suggested that preferential ipso attack at C_3 in **7** can be explained by cyclopropane stabilization of a Wheland-type transition state, which would invalidate this reaction as a useful precedent for inductive deactivation of an ipso position by cyclopropyl. We note that (a) there is evidence to indicate that the cyclopropane ring in **7** is in nearly the worst possible geometry for conjugative interaction with the benzene π system,[19] and (b) this situation is not greatly improved in the Wheland intermediate (model inspection). Thus, in our view, inductive deactivation by cyclopropyl remains a viable factor in nitration of **7**.

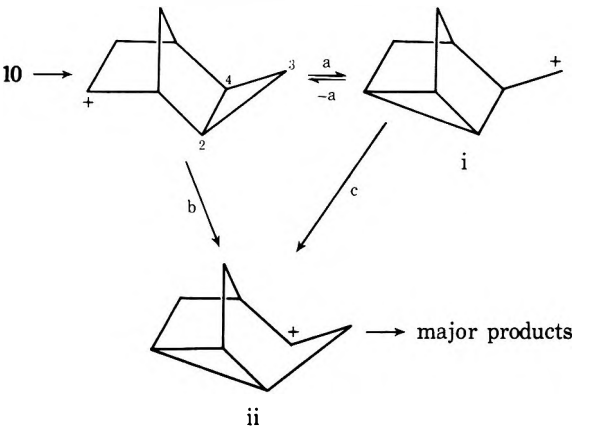
(19) (a) R. C. Hahn, P. H. Howard, S.-M. Kong, G. A. Lorenzo, and N. L. Miller, *J. Am. Chem. Soc.*, **91**, 3558 (1969); (b) R. C. Hahn and P. H. Howard, *ibid.*, **94**, 3143 (1972).

(20) M. A. Battiste and M. E. Brennan, *Tetrahedron Lett.*, 5857 (1966).

(21) S. Terabe and R. Konaka, *J. Am. Chem. Soc.*, **95**, 4976 (1973).

(22) C. K. Ingold and F. R. Shaw, *J. Chem. Soc.*, 2918 (1927).

(23) The question of relative magnitudes of 2,3- and 2,4-bond participation has been raised by a referee. Studies[24,25] of a reaction which generates a stereoelectronically similar system (solvolysis of brosylate **10**; see text) can be interpreted as sources of evidence for either mode of participation, depending on whether one regards step b or steps (a + c) as a more facile route to species ii (below). Our preference for step b is based on the facts



that i is a primary cation whereas ii is secondary, and cyclopropyl σ-route migration to a C^+ center (step c) is not facile relative to processes involving C–C ring bonds (see comments in ref 25).

(24) K. B. Wiberg and G. R. Wenzinger, *J. Org. Chem.*, **30**, 2278 (1965).

(25) J. A. Berson, R. G. Bergman, G. M. Clarke, and D. Wege, *J. Am. Chem. Soc.*, **91**, 5601 (1969).

(26) Cf. C. MacLean and E. L. Mackor, *Mol. Phys.* **4**, 241 (1961).

Estimations of van der Waals Strain in Hydrocarbons

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Evaluation of van der Waals strain can in principle be based on enthalpies of formation of appropriate reference compounds. However, experimental enthalpies are available for molecules exhibiting only relatively restricted ranges of crowding. A potentially useful source of further data may be found in relative reaction rates of crowded molecules.

Recent studies have shown encouraging success in calculating steric retardation and steric acceleration.[1–6] These have been based ultimately on calculation of enthalpies of formation of model compounds, and more specifically on calculation of relative differences in strain energy between some model of the reactant system and some model of the transition state.

A wide variety of methods has been proposed for estimating enthalpies of formation of alkanes and cycloalkanes; these are, of course, methods of interpolation and extrapolation from experimental values.[7–17]

We have made a careful evaluation of four representative methods for estimating the strain energy component of alkanes (primarily van der Waals) and have explored the usefulness of two criteria for judging effectiveness: (1) the accuracy with which the method reproduces experimental ΔH_f^0 values, and (2) the accuracy with which it treats relative rates of reactions controlled primarily by steric factors. We conclude that accuracy of reproducing ΔH_f^0 values is at present an insufficient criterion; methods which are expected a priori to give a poor account of strain energy may yield quite good ΔH_f^0 values. The problem lies in three facts: (1) that for alkanes the strain energy component is a small (and variable) fraction of the total ΔH_f^0, (2) that the six or more adjustable constants employed in each method tend to absorb the strain components in nonspecific ways, and (3) that accurate experimental ΔH_f^0 values exist for rather few strained molecules, the available data making relatively modest demands on any method of calculating ΔH_f^0. We have evaluated the Franklin protocol,[15] a simple and relatively effective older method which treats strain effects very roughly, the Allen protocol,[16,17] which reproduces experimental ΔH_f^0 values well, and molecular mechanics using two of the several available good alkane force fields, Allinger 1971[13] and Schleyer 1973.[12] The list we have treated includes most of the alkanes and methyl-substituted alkanes for which accurate experimental ΔH_f^0 values are reported.[9] The results are shown in Figures 1a–c. The standard deviations and correlation coefficients are as follows: Franklin, 0.6, 0.998; Allen, 0.3, 0.999; Schleyer, 0.7, 0.998; Allinger (not shown), 0.4, 0.999. The molecular mechanics data are based on our calculations (a) of steric energies, (b) of statistical mechanical corrections,[18] and (c) of reparameterized group increment values.[5] Each of the four methods does a good job overall in predicting ΔH_f^0 for the reference compounds. The problem may now be presented by reference to Figures 2a–c. These show what happens when a series of considerably more hindered alkanes is treated by the same methods. Each point in Figure 2 is based on a difference, $\Delta\Delta H_f^0 = \Delta H_f^0[RC(CH_3)_3] - \Delta H_f^0[RCH(CH_3)_2]$ for a neoalkane and an isoalkane. Experimental data are available for just a few of the 36–40 alkanes represented in the figure. The log k_{rel} are the Taft E_s values representing steric hindrance;[19] $k_{rel} = k/k_0$ where k is rate of hydrolysis of any ester RCOOEt

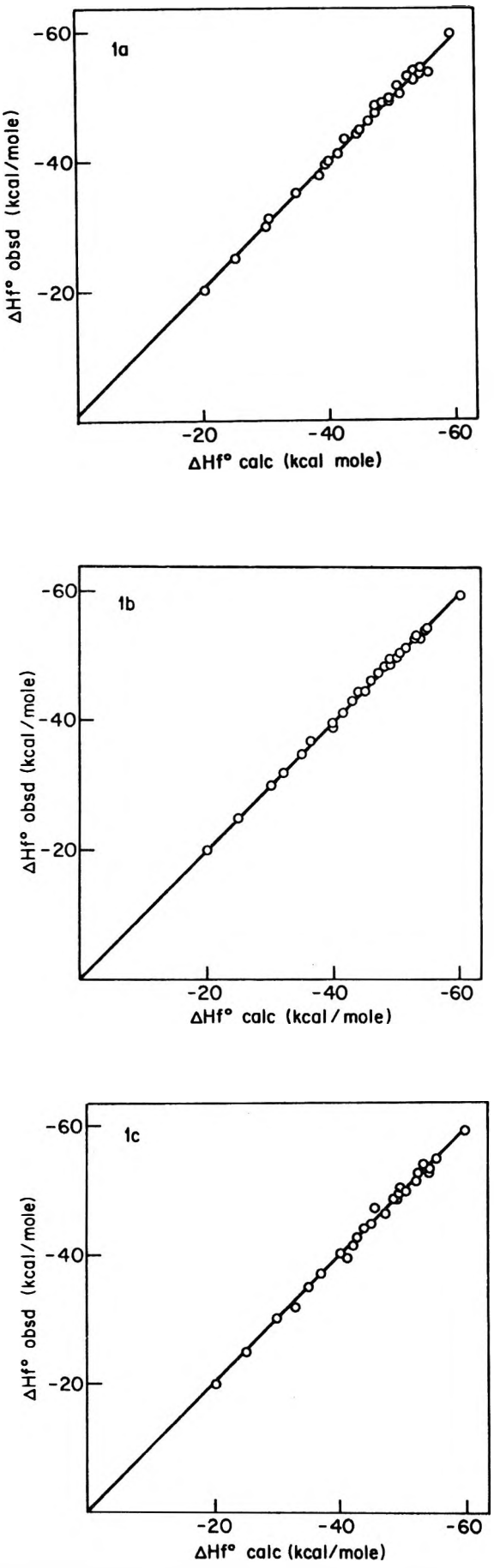

Figure 1. Observed heat of formation (ΔH_f^0) vs. calculated heat of formation (gas, 298 °C) for various alkanes; (a) using Franklin protocol,[15] (b) using Allen protocol,[16,17] (c) using molecular mechanics with Schleyer 1973[12] force field.[5,6] The Allinger 1971 force field gives a generally comparable plot. These data are from ref 6.

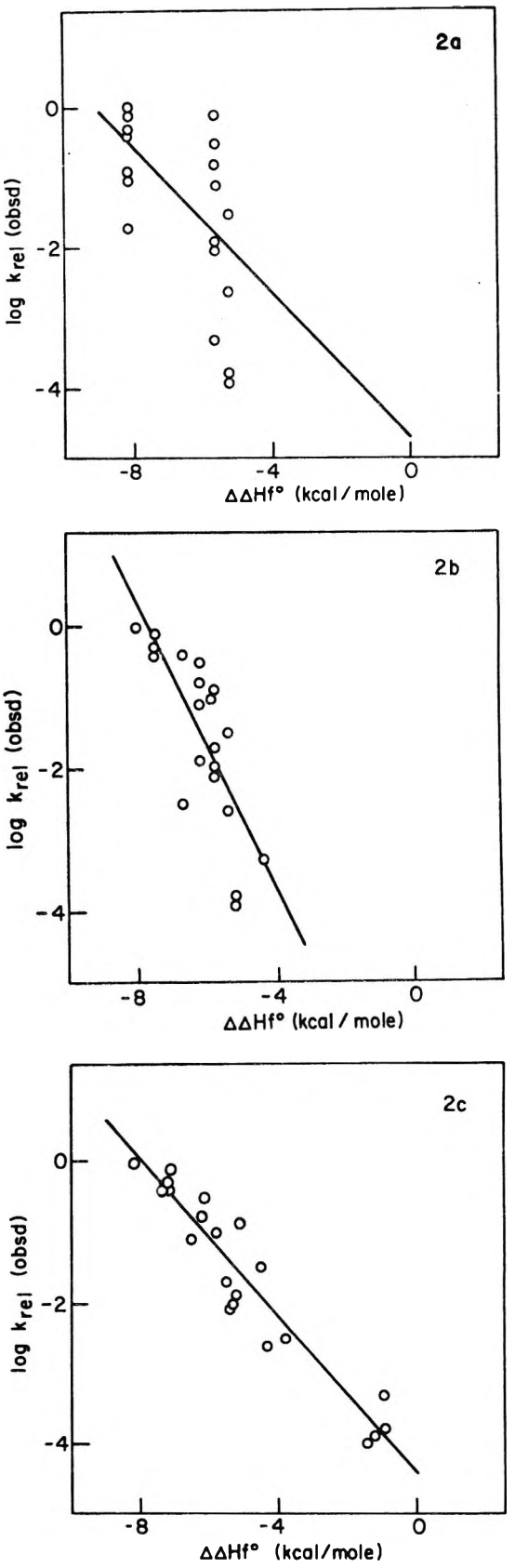

Figure 2. The strain energy component of the calculated ΔH_f^0 values of Figure 1 as shown by plot of Taft E_S values ($-\log k_{rel}$)[18] vs. $\Delta\Delta H_f^0$ where $\Delta\Delta H_f^0 = \Delta H_f^0$ (neoalkane) $- \Delta H_f^0$ (isoalkane); using ΔH_f^0 calculated (a) by the Franklin protocol, (b) by the Allen protocol, and (c) by molecular mechanics with the Schleyer force field. The Allinger 1971 force field gives a generally comparable plot. In 2c we have omitted points for cyclobutanecarboxylic acid and for cyclopentanecarboxylic acid, for which the isoalkane–neoalkane model breaks down, and for dineopentylacetic acid, for which the Schleyer and the Allinger force field calculation fails on the model hydrocarbons. The data are from ref 6.

Table I. Alkanes Used to Get Calibration Terms

	Registry no.	$-\Delta H_f^0$ (298)[a] exptl	SM[b]	Lowest[d] energy conformer Exptl	Lowest[d] energy conformer Calcd	"Exptl"[e] strain energy	SE[f] (Schleyer)	SE[g] strainless (Schleyer)	SE[h] (Allinger)	SE[i] strainless (Allinger)
Pentane	109-66-0	−35.00	0.39	−35.39	−35.46	0.07	2.94	2.92	4.33	4.34
Hexane	110-54-3	−39.96	0.63	−40.59	−40.61	0.02	3.52	3.50	4.95	4.95
Heptane	142-82-5	−44.88	0.86	−45.74	−45.77	0.03	4.10	4.07	5.56	5.56
Octane	111-65-9	−49.82	1.10	−50.92	−50.92	0.00	4.67	4.64	6.17	6.17
Nonane	111-84-2	−54.74	1.33	−56.07	−56.07	0.00	5.24	5.21	6.77	6.78
Decane	124-18-5	−59.67	1.57	−61.24	−61.22	−0.02	5.81	5.79	7.38	7.39
Undecane	1120-21-4	−64.60	1.80	−66.40	−66.38	−0.02				
Dodecane	112-40-3	−69.52	2.04	−71.56	−71.53	−0.03				
2-MeC4	78-78-4	−36.92	0.09	−37.01	−37.55	0.54	3.80	3.08	3.47	2.78
2-MeC5	107-83-5	−41.66	0.27	−41.93	−42.71	0.78	4.38	3.65	4.11	3.39
2-MeC6	591-76-4	−46.59	0.52	−47.11	−47.86	0.75	4.93	4.23	4.69	4.00
2-MeC7	592-27-8	−51.50	0.76	−52.26	−53.01	0.75	5.50	4.80	5.30	4.61
2,2-Di-MeC4	75-83-2	−44.35	0.00	−44.35	−45.69	1.34	5.03	3.62	1.91	0.53
2,2-Di-MeC5	590-35-2	−49.27	0.12	−49.39	−50.85	1.46	5.59	4.20	2.55	1.14

[a] References 9–11. [b] Statistical mechanical correction, ref 18. [c] Column 2 − column 3, "experimental" energy of conformer of lowest energy. [d] $-10.000\,n(CH_3) - 5.153\,n(CH_2) - 2.400\,n(CH) - 0.540\,n(C)$. [e] Nominal values are 0 for *n*-alkanes, 0.70 for isoalkanes, 1.40 for neoalkanes. Deviations from the nominal represent experimental error or departures from the assumed model. [f] Steric energy from Schleyer 1973 force field, ref 12. [g] $0.602\,n(CH_3) + 0.573\,n(CH_2) + 0.700\,n(CH) + 0.643\,n(C)$. The difference between the SE columns should match the value in the exptl strain energy column. [h] From Allinger 1971 force field, ref 13. [i] $1.254\,n(CH_3) + 0.610\,n(CH_2) - 1.595\,n(CH) - 5.101\,n(C)$.

and k_0 is the corresponding rate for ethyl acetate. The neoalkane has been taken as a model of the transition state in formation of tetrahedral intermediate, the isoalkane as model of the starting ester. Remarkably enough the energy differences, $\Delta\Delta H_f^0$, calculated by molecular mechanics for these alkanes in the gas phase show a good correlation with ester hydrolysis rates.[5]

Use of better models, RCOOH and $RC(OH)_3$, respectively, gives even better correlations.[6] However, these better models unfortunately require introduction of several ad hoc constants into the alkane force fields. (The Franklin and Allen protocols are not applicable to these oxygen-containing models.)

It is relatively clear from Figure 2 and verifiable by the statistics that molecular mechanics ΔH_f^0 values based on the Schleyer force field, though showing the poorest correlation with ΔH_f^0 experimentally, are greatly superior to the empirical Allen protocol values when applied to these highly hindered compounds. Results are as follows: Franklin protocol correlation coefficient, −0.57; Allen, −0.76; Schleyer, −0.95; Allinger, −0.93.

Results and Discussion

There have been many definitions of strain energy;[12-14] most are based on ΔH_f^0 values for the first members of the alkane series. Since for present purposes it is clearly necessary to seek the highest possible precision, we have explored a modified definition of strain based on the alkanes listed in Table I. In our definition, all strain values are related to the *n*-alkane single conformation of lowest energy and make use of an extended set of statistical mechanical corrections.[18] We define strain as follows: *n*-alkane, fully extended, zero strain; isoalkane, 0.70 kcal/mol; terminal neoalkane, 1.40 kcal/mol. These values are consistent with differences in observed enthalpies.[9] There are certain advantages in skipping over the first members of each series since these prove exceptional when enthalpy correlations are attempted.[9]

The column labeled "Exptl" strain energy shows how small are the deviations of calculated strain from the defined strain values of 0, 0.70, and 1.40; the standard deviation is about 0.06 kcal/mol. The group increment values in footnote *d* therefore provides a good account of the strain-free component of ΔH_f^0 for alkanes.

A molecular mechanics calculation leads to a "steric energy" for a given conformation. The steric energy may be dissected into a strain energy component and a "base" energy component which may be computed from the usual group increments. The "base" component depends on how the force field has been defined. To focus on this dissection we have calculated group increments which give the "base" component of the steric energy for the Schleyer and the Allinger force fields: Table I, footnotes *g* and *i*.

In Table II are summarized values for the first members of the alkane series, for many of the relatively strained alkanes for which data are available, and for a few cyclic compounds. It can be seen that strain energy amounts to from 0 to 150% of the steric energy depending upon compound and force field. It further turns out that plots of differences in experimental and calculated strain energies (Δ column of Table II) vs. differences in observed and calculated ΔH_f^0 show rather poor correlations.

Relatively few alkane strain energy values in Tables I and II have been previously reported, and it is for this reason that we included the cyclic compounds. Agreement is relatively good with Allinger strain values based on a different definition,[13] the largest difference being about 0.5 kcal/mol. Differences with the Schleyer definition of strain are larger; some are more than 1.4 kcal/mol.

Differences between "observed" and "raw" calculated strain energies expressed as standard deviations are Franklin (not tabulated), 1.0; Allen (not tabulated), 0.7; Schleyer, 1.0; Allinger, 0.7. These do not parallel the results shown in Figure 2.

Inspection of the "raw" calculated strain energies suggests that some may be biased. One way to express this is to state that the line $y = mx + b$ where y is an unbiased estimate of calculated strain energy for a given value of x, the "raw" calculated strain energy, may not have a slope of 1 and an intercept of 0. We therefore calculated m and b for each case and obtained the following standard deviations for ("observed" strain energy − y): Franklin, 1; Allen 0.4; Schleyer, 0.6; and Allinger, 0.4. Even with this improvement the differences are hardly as striking as those in Figure 2.

Table II. Representative Strain Energies for Alkanes

	Registry no.	ΔH_f[a] exptl	SM[b] corrn	ΔH_f[c] strainless	"Exptl"[d] strain energy	SE[e] MM (Schleyer)	SE[f] strainless (Schleyer)	Strain[g] energy calcd (Schleyer)	Δ[h] (Schleyer)	SE[i] MM (Allinger)	Strainless (Allinger)	Strain[g] energy calcd (Allinger)	Δ[h] (Allinger)
Ethane	74-84-0	−20.24	0.00	−20.00	−0.24	1.04	1.20	−0.16	−0.08	2.37	2.51	−0.14	−0.10
Propane	74-98-6	−24.82	0.00	−25.15	0.33	1.72	1.78	−0.06	0.39	3.08	3.12	−0.04	0.37
Butane	106-97-8	−30.15	0.27	−30.31	−0.11	2.35	2.35	−0.01	0.11	3.71	3.73	0.02	−0.09
Isobutane	75-28-5	−32.15	0.00	−32.40	+0.25	2.08	2.51	−0.43	0.68	2.10	2.17	−0.07	0.32
Neopentane	463-82-1	−39.67	0.00	−40.54	0.87	2.16	3.05	−0.89	1.76	−0.38	−0.09	−0.29	1.16
2,3-DiMeC4	79-29-8	−42.49	0.27	−44.80	2.04	6.28	3.81	2.47	−0.43	3.85	1.83	2.02	0.02
2,3-DiMeC5	565-59-3	−47.62[j]	0.40	−49.95	1.93	8.89	4.38	4.51	−2.58[j]	5.91	2.44	3.47	−1.54[j]
2,4-DiMeC5	108-08-7	−48.28	0.11	−49.95	1.56	5.66	4.38	1.28	0.28	3.66	2.44	1.22	0.34
2,5-DiMeC6	592-13-2	−53.21	0.26	−55.11	1.64	6.50	4.95	1.55	0.09	4.69	3.05	1.64	0.00
2,2-DiMeC6	590-73-8	−53.71	0.38	−56.00	1.91	6.12	4.77	1.35	0.56	3.10	1.75	1.35	0.56
2,2,3-TriMeC4	464-06-2	−48.95	0.00	−52.94	3.99	8.68	4.35	4.33	−0.34	3.00	−0.43	3.43	0.56
2,2,4-TriMeC5	540-84-1	−53.57	0.03	−58.09	4.49	8.91	4.93	3.98	0.51	4.20	0.18	4.02	0.47
2,2,3-TriMeC5	564-02-3	−52.61	0.20	−58.09	5.28	10.92	4.93	5.99	−0.71	4.81	0.18	4.63	0.65
2,2,3,3-TetraMeC4	594-82-1	−53.99	0.00	−61.08	7.09	12.41	4.90	7.51	−0.42	3.08	−2.68	5.76	1.33
2-Me3Et-C5	609-26-7	−50.48	0.43	−55.11	4.20	10.84	4.95	5.89	−1.69	7.38	3.05	4.33	−0.13
Cyclopentane	287-92-3	−18.46	0.00	−25.77	7.31	(11.03)	2.87	8.16	−0.85	(11.76)	3.05	8.71	−1.40
Cyclohexane	110-82-7	−29.43	0.00	−30.92	1.49	6.00	3.44	2.56	1.07	5.94	3.66	2.28	−0.79
cis-Decalin	493-01-6	−40.38	0.00	−46.02	5.98	(11.97)	5.98	5.99	−0.35	(8.06)	1.69	6.37	−0.73
trans-Decalin	493-02-7	−43.52	0.00	−46.02	2.45	(9.26)	5.98	3.28	−0.83	(5.48)	1.69	3.79	−1.34
Norbornane[k]	279-23-2	−12.60	0.00	−30.57	17.97	21.23	4.27	16.97	1.01	18.12	−0.14	18.26	−0.29
Adamantane[l]	281-23-2	−32.96	0.00	−40.52	7.56	(14.06)	6.24	7.82	−0.26	(5.00)	−2.72	7.72	−0.16

[a] References 9–11. [b] Statistical mechanical correction, ref 18. [c] Footnote *d*, Table I. [d] Column 5 + column 4 − column 3. [e] Schleyer 1973, ref 12, or Allinger 1971 force field, ref 13. Values in parentheses calculated from Tables II and VI, ref 12. [f] Footnote *g*, Table I. [g] SE(MM) − SE(strainless). [h] "Exptl"—calcd strain energy. [i] Footnote *i*, Table I. [j] Comparison of related compounds suggests that literature ΔH_f^0 (298) is about 0.6 kcal/mol too negative. [k] Reference 20. [l] Reference 21. Other values are −30.65 (ref 22) and −30.57 (ref 23).

Everyone agrees that force fields are going to undergo further refinement, and such refinements may lead to some further improvements of calculated ΔH_f^0 values. However, the larger issue involved in finding data for calibrating the van der Waals terms of force fields remains: there are not enough good ΔH_f^0 data for highly crowded molecules.

We therefore suggest that it may prove useful to adopt a different approach, taking obvious precautions to avoid circular reasoning. We may assume that the Taft E_s values are a generally good measure of steric hindrance, and may then use carefully chosen reaction series for providing additional values of van der Waals strain. This argument is, of course, the exact converse of the one we have used previously.[5,6] Data pertaining to van der Waals forces are even scarcer for compounds other than alkanes, and carefully selected reaction data may provide a valuable additional set of reference values.

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Prototropic Equilibrium of Imines. *N*-Benzylidene Benzylamines

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The 1,3-prototropic shift of imines, exemplified in isomerization of unsymmetrically substituted *N*-benzylidene benzylamines, has been reexamined. Equilibrium constants for para-monosubstituted systems were determined by NMR methods; the constants do not show the anomalies reported in older work, and are adequately correlated by the Hammett equation ($\rho = 0.94$).

Recent investigations[1] of prototropic equilibration of nitrones Ia ⇄ Ib (Behrend rearrangement) in this laboratory invited a comparison with the corresponding imines, IIa ⇄ IIb. Imine isomerization had been investigated by Shoppee,[2,3]

$$\mathrm{ArCH_2{-}NX} \rightleftharpoons \mathrm{ArCH{=}NX}$$
$$\mathrm{CHAr'} \qquad\qquad \mathrm{CH_2Ar'}$$

Ia, IIa Ib, IIb

Ia, Ib, X = oxygen atom; IIa, IIb, X = electron pair

who brought about equilibration by heating *N*-benzylidene benzylamines with sodium ethoxide solution, over 40 years ago. His results on the effect of substituents, particularly alkyl groups, played a role in the early development of the theory of hyperconjugation.[4] Much later, the mechanism of isomerization was investigated by Cram and Guthrie,[5] who showed that it probably involved formation of a delocalized carbanion, rather than the synchronous process originally proposed.

In the ensuing years, uncertainties developed about the interpretation of the equilibrium constants reported by Shoppee. Baker in 1952 stated that the effects of substituents could not be satisfactorily assessed.[6] The effects of para substituents were not acceptably consistent with the correlations subsequently developed by Hammett, and could not be satisfactorily interpreted according to theories of electronic influences. The equilibrium constant for the *p*-methyl substituent, of particular importance for hyperconjugation in its earliest development, was especially inconsistent.

At the time of Shoppee's investigations, most instrumental methods of analysis had not been developed. As a consequence, he had to use an indirect and error-prone analytical method to determine the composition of the equilibrium mixtures of imines. He hydrolyzed the imines, converted the resulting benzaldehydes to dinitrophenylhydrazones, and compared the melting range of these mixtures with the phase diagram determined from known mixtures. Although this method is in principle sound, its reliability is vitiated if unsuspected traces of a third component should be present; it is also potentially sensitive to variations in yield of the conversion to dinitrophenylhydrazones. It therefore seemed desirable to reinvestigate the subject, not only for comparison with the Behrend rearrangement, but because of the importance of imine tautomerism in synthesis and in biological transamination.

We have prepared a series of para-substituted *N*-benzylidene benzylamines, all of which are known, by warming the corresponding benzaldehydes and benzylamines together. The purified imines consisted of but a single geometrical isomer, insofar as we could determine by infrared and NMR spectroscopy, consistent with Ossorio's report[7] that only the anti isomer is present significantly at equilibrium. We did not include the *p*-nitro substituent, although we would have liked to, because its reaction with sodium ethoxide is more complex (a nitronate salt is apparently formed, and is the basis for a microanalytical determination of benzylamine[8]).

We equilibrated the imines by refluxing them in a 1 M solution of sodium ethoxide in absolute ethanol for periods of 2–36 h. Analysis of the mixtures was accomplished with NMR spectroscopy. Neither the methylene nor the methyne hydrogens of the pairs of tautomers were sufficiently well resolved, unfortunately. However, the methyl signals of the mixtures from the *p*-methyl, *p*-methoxy, and *p*-dimethylamino systems allowed their compositions to be determined. For the *p*-chloro system, hydrolysis of the imines to the corresponding mixture of benzaldehyde and *p*-chlorobenzaldehyde was necessary; the signals of the aldehyde protons were separated by 2.5 Hz.

For each substituent, equilibrium was approached from both sides, and values were determined at a series of times to be sure that equilibrium had been reached. The mean values

Table I. Equilibrium Constants for Tautomerism of Imines and Nitrones

p-$RC_6H_4CH{=}N(Y)CH_2C_6H_5 \rightleftarrows p$-$RC_6H_4CH_2N(Y){=}CHC_6H_5$
A B

	Imines (Y = e_2)			Nitrones (Y = O)
R	K (found)[a]	K (lit.[3])	Log K	K
$(CH_3)_2N$–	0.17	0.149	−0.77 ± 0.03	
CH_3O–	0.55	0.370	−0.26 ± 0.02	0.33
CH_3–	0.67	1.22	−0.17 ± 0.02	0.61
Cl–	1.64	1.13	0.214 ± 0.004	0.62

[a] K = B/A.

slope corresponding to ρ = 0.941 ± 0.008. Figure 1 also includes two values determined by Baker, Nathan, and Shoppee[4] for the *tert*-butyl and isopropyl groups, which they used in comparison with Shoppee's value for the methyl group to establish a relative order of hyperconjugation effects of alkyl groups.

One can conclude that tautomerism of imines is not anomalous, nor is the effect of the p-methyl group on it. The behavior of the system is adequately encompassed by the Hammett equation. The situation with analogous nitrones, Ia ⇄ Ib, has recently been analyzed in a way that implies that substituent effects operate in an ambivalent way with them, owing to the semipolar N–O bond, and that equilibrium constants for the Behrend rearrangement should not parallel

Table II. Properties of Imines (Benzylidene Benzylamines)

$ArCH_2$–N=CHAr′

	Substituent on			NMR, δ, ppm (CCl_4, Me_4Si)			
Registry no.	Ar	Ar′	Mp, °C	–CH=N–	Arom CH	$-CH_2N$	$-CH_3$
24431-17-2	H	p-$(CH_3)_2N$	74–76 (lit.[3] 75)	8.13	7.10 (q, 4 H), 7.22 (s, 5 H)	4.67	2.94
31401-61-3	p-$(CH_3)_2N$	H	55.5–57 (lit.[3] 57)	8.02	6.70 (q, 4 H), 7.36 (m, 5 H)	4.60	2.76
622-72-0	H	p-CH_3O	42–43 (lit.[2] 42)	8.13	7.15 (q, 4 H), 7.16 (s, 5 M)	4.68	3.73
31490-38-7	p-CH_3O	H	Oil[2]	8.12	6.86 (q, 4 H), 7.40 (m, 5 H)	4.61	3.67
24431-15-0	H	p-CH_3	26–27 (lit.[3] 27)	8.11	7.15 (s, 5 H), 7.27 (q, 4 H)	4.67	2.32
41882-47-7	p-CH_3	H	bp 124 (0.2 mm) [lit.[3] 190–196 (20 mm)]	8.03	6.94 (s, 5 H), 7.1–7.7 (m, 4 H)	4.60	2.26
13540-93-7	H	p-Cl	34 (lit.[3] 34)	8.11	7.10 (s, 5 H), 7.11–7.7 (m, 4 H)	4.62	
15383-71-8	p-Cl	H	35–36 (lit.[3] 36–37)	8.28	6.71 (s, 5 H), 7.52 (q, 4 H)	4.77	

are given in Table I, along with the values reported by Shoppee. (The results of individual determinations are in Table III.)

Although our results differ quantitatively from those of Shoppee, the relative effects of substituents are the same if one omits the value for p-methyl, which is markedly out of line. A graphic comparison is given in Figure 1 as a Hammett plot vs. σ;[9] the weighted least-squares method[10] gave a line of

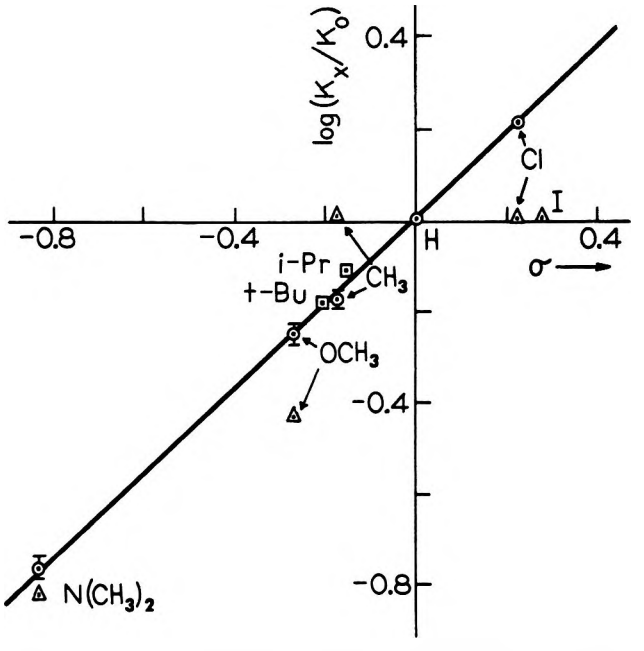

Figure 1. Hammett plot of equilibrium ratios in imine isomerizations: ⊙, data from present work; △, data of Shoppee;[3] □, data of Baker, Nathan, and Shoppee.[4]

Table III. Isomerization of Imines

p-$RC_6H_4CH{=}N$–$CH_2Ph \rightleftarrows p$-$RC_6H_4CH_2$–N=CHPh
A B

Initial imine			
R	A or B	Time, h	Product ratio, B/A
$(CH_3)_2N$	A	5	0.18
$(CH_3)_2N$	A	6	0.16
$(CH_3)_2N$	A	7	0.16
$(CH_3)_2N$	A	12	0.18
$(CH_3)_2N$	B	2.25	0.17
$(CH_3)_2N$	B	3.5	0.18
CH_3O	A	8–36	0.57[a]
CH_3O	B	5–12	0.53[a]
CH_3	A	5–13	0.69[a]
CH_3	B	4–5	0.65[a]
Cl	A	16–36	1.63[a]
Cl	B	20–29	1.64[a]

[a] Mean of values recorded after equilibrium was reached.

those of imines.[1] This conclusion is consistent with the results reported here, as can be seen by comparing the values for nitrones and imines given in Table I.

Experimental Section

Imines. The appropriate aldehydes and benzylamines (slight excess), all of which are commercial products, were heated for 30 min at 100 °C, essentially following the method of Shoppee.[3] The resulting crude imines were dissolved in ethyl ether and washed successively with two portions of 2% acetic acid, two portions of 10% sodium bicarbonate solution, and one portion of water. Evaporation of the dried (Na_2SO_4) solutions left the imines, which were recrystallized from petroleum ether or ligroin when possible. The identity of these known compounds was confirmed by their NMR spectra, all of which showed an upfield doublet and a downfield triplet with J = 1.3–1.5 Hz, at-

tributable to the $-CH_2N{=}CH-$ system, an aromatic region differentiated into 4 H and 5 H parts, and singlet signals appropriate to the substituents. These data are collected in Table II.

Isomerization. Solutions of 0.3 g of imine in 20 ml of 1 N ethanolic sodium ethoxide were heated under reflux (solution temperature 82 °C). Reaction was quenched at a determined time by rapid cooling with cold water and dilution with 20 ml of distilled water. The resulting mixtures were extracted twice with chloroform, and the extracts were washed twice with water and then dried over sodium sulfate.

Analysis. The dried chloroform solutions were evaporated under vacuum and the residue was dissolved in carbon tetrachloride containing 1% Me_4Si. NMR spectra were determined on a Varian T-60 instrument. Addition of a drop of Me_2SO-d_6 or CD_3OD enhanced the resolution of the signals of the pairs of isomers present. The intensities of the methyl signals (where present; see Table II) were compared to obtain the ratios reported in Table III. In general, three to five samples of each imine were used; except for the *p*-dimethylamino pair, for which all samples are reported, only the mean values are shown.

The mixtures with a *p*-chloro substituent were first hydrolyzed by emulsifying with a small amount of methanol–water mixture and heating with 30 ml of 2 N sulfuric acid at 100 °C for 30 min. The cooled mixture was then extracted with ether, the dried extracts were evaporated to dryness, and the residue was taken up in carbon tetrachloride for NMR analysis by comparison of the aldehydic CH signals.

The reliability of the methods was examined by using mixtures of known compositions. For the pair *N*-benzylidene-*p*-methylbenzylamine/*p*-methylbenzylidenebenzylamine, the results follow: known, 59.5/40.5 (found, 59.8/40.2); known, 58.2/41.8 (found, 59.5/40.5); known, 55.9/44.1 (found, 56.1/43.9). For benzaldehyde/*p*-chlorobenzaldehyde mixtures derived from the *p*-chloro tautomeric imines, the results follow: known, 61.1/38.9 (found, 62.0/38.0); known, 62.4/37.6 (found, 63.0/37.0).

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Occurrence of N-Alkylation during the Acidolytic Cleavage of Urethane Protecting Groups[1a,b]

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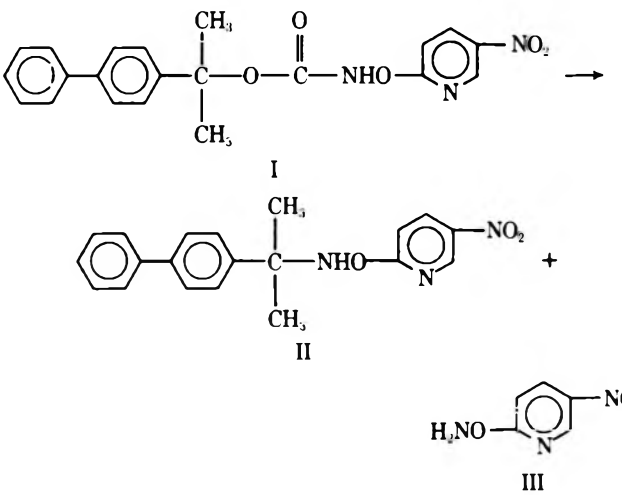
The occurrence of N-alkylation as a side reaction during the acidolytic cleavage of urethane protecting groups by trifluoroacetic acid has been investigated under the conditions of solid phase peptide synthesis. N-Alkylation did not occur when the protecting group was *tert*-butyloxycarbonyl (Boc) as treatment of Boc-Gly-Lys(Z)-resin with 50% CF_3COOH–CH_2Cl_2 did not produce *t*-Bu-Gly-Lys(Z)-resin (<0.05%). This novel side reaction did occur when the protecting group was benzyloxycarbonyl (Z). When Boc-Lys(Z)-resin was treated with 50% CF_3COOH for 14 h (25 °C) the Z group was partially removed and gave rise to 0.6% N^{ϵ}-benzyllysine-resin. The use of a more acid stable N^{ϵ} protecting group (2,4-Cl_2Z) suppressed N-alkylation to less than detectable levels (<0.1%). The acidolytic removal of the benzyloxycarbonyl group from Z derivatives in solution was also studied. Treatment of Z-Gly and Lys(Z) (0.1 M) in refluxing CF_3COOH (30 min) gave 1.1% Bzl-Gly and 3.3% Lys(Bzl), respectively. The addition of 20% anisole gave 0.5% Bzl-Gly and 2.1% Lys(Bzl) from the same Z derivatives. The use of CF_3SO_3H–CF_3COOH–anisole (30 min, 25 °C) allowed the formation of 1.2% Bzl-Gly from Z-Gly and 3.1% Lys(Bzl) from Lys(Z). No N-alkylation could be detected when amino acid resins or free amino acids containing Z protecting groups were cleaved with anhydrous HF.

The most widely used amino protecting groups in peptide synthesis are the benzyloxycarbonyl (Z)[2] and *tert*-butyloxycarbonyl (Boc)[3] groups. A recent addition to this family of urethane-type protecting groups is the relatively acid-labile biphenylisopropyloxycarbonyl (Bpoc)[4,5] group. A report[6] of N-alkylation during the acidolytic cleavage of a Bpoc group from a derivative of hydroxylamine initially prompted the present study as a possible explanation of a rise in background observed with picrate monitoring during solid phase peptide synthesis.[7]

The unexpected formation (20%) of *N*-2-(*p*-biphenylyl)-isopropyl-*O*-(5-nitro-2-pyridyl)hydroxylamine (II) occurred when 2-(*p*-biphenylyl)isopropyl *N*-(5-nitro-2-pyridyloxy)-carbamate (I) was treated with acetic acid in nitromethane.[6] Attack of III by *p*-biphenylyldimethyl carbonium ion could give rise to II. Attack of the carbonium ion on the carbamic acid formed from I, with simultaneous decarboxylation, was also considered a possible route to II.

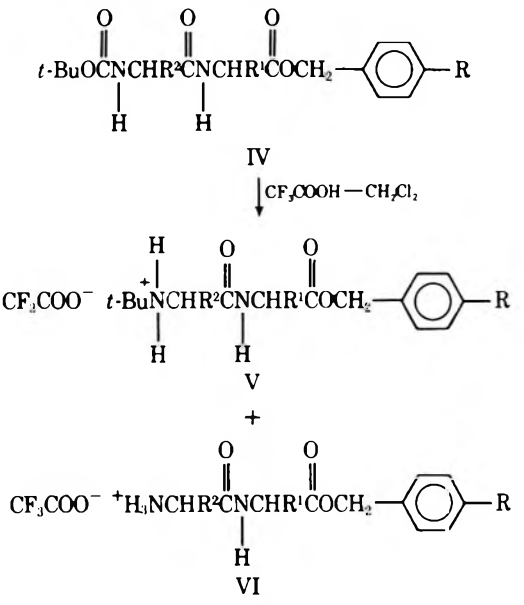


I

II

III

Our initial interest was focused on the possible occurrence of an analogous reaction with the Boc group under conditions of solid phase peptide synthesis. The formation of a small amount (ca. 0.1–1%) of N^{α}-*tert*-butyl peptide (V) during each

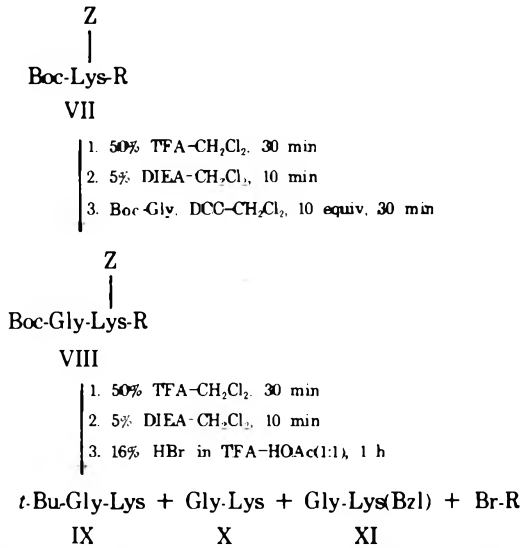


deprotection step is undesirable because it would give rise to terminated chains or *N*-alkyl peptides. In addition, the production of a variable amount of hindered secondary amines would give corresponding increases in background if a chloride[8] or picrate[9] monitoring method were used to follow the course of a solid phase peptide synthesis.

Results and Discussion

To detect the occurrence of low levels of such side reactions, a sensitive model system employing Boc-Lys(Z)-resin (VII) was devised (see Chart I). The presence of lysine, with α- and

Chart I[a]



[a] Model system for the detection of N$^{\alpha}$-*tert*-butylation and N$^{\epsilon}$-benzylation during solid phase peptide synthesis. TFA, trifluoroacetic acid; DIEA, diisopropylethylamine; HOAc, acetic acid; DCC, *N,N'*-dicyclohexylcarbodiimide; R, ring-brominated oxymethylcopoly(styrene–1% divinylbenzene).

ϵ-amino groups that can react with ninhydrin, allows the detection of reaction products having either the α or ϵ position blocked. For chromatographic reference *t*-Bu-Gly-Lys (IX) was prepared by treating N^{α}-chloroacetyl-N^{ϵ}-Z-L-lysine[10] with *tert*-butylamine followed by decarbobenzoxylation in refluxing TFA.[11] Similarly, Gly-Lys (X) was obtained starting with N^{α}-chloroacetyl-N^{ϵ}-Z-L-lysine and ammonium hydroxide.[10] Compounds IX and X are well resolved on the long column of an amino acid analyzer, thereby allowing the detection of small amounts (≥0.05%) of IX in an overloaded sample containing large amounts of X. The use of an amino acid analyzer for the detection of small quantities of amino acids and peptides in the presence of large amounts of similar compounds has been described elsewhere.[12,13]

Table I. Reaction of Boc-Lys(Z)-R[a] with Cleavage Reagents

Run		Time, h	N^{ϵ}-Bzl-Lys, mol %[b]
1	5% TFA–CH_2Cl_2 (v/v)	14	0
2	50% TFA–CH_2Cl_2 (v/v)	14	0.67
3	TFA	14	2.56
4	16% HBr in TFA–HOAc (1:1)[c]	1	0
5	HF	1	0

[a] R represents ring-brominated oxymethylcopoly(styrene–1% divinylbenzene).[9] Initial substitution of resin was 0.457 mmol Lys/g. The reactions used 0.100–0.200 g of resin in 2–4 ml of cleavage solution and were run at room temperature. [b] The resins obtained from runs 1–3 were washed with CH_2Cl_2, dried, and then hydrolyzed in HCl–C_2H_5COOH. The values obtained for runs 1–3 have been corrected for the production of 0.34 mol % N^{ϵ}-Bzl-Lys which occurred when untreated Boc-Lys(Z)-R was hydrolyzed in HCl–propionic acid. The hydrolysates were analyzed on the short column (0.9 × 7 cm PA-35 sulfonated polystyrene, sodium citrate buffer, pH 7.0, 66 ml/h, 56 °C) of a Beckman 120B amino acid analyzer. The cleavage products from runs 4 and 5 were chromatographed without further treatment. Limit of detection was 0.1 mol %. [c] One volume of 32% HBr–HOAc was added to Boc-Lys(Z)-R that was suspended in one volume of TFA.

The protected dipeptide-resin (VIII) was deprotected, neutralized, and cleaved as indicated in Chart I. Analysis of the cleavage products relative to Gly-Lys (100%) gave Lys (0.16%), and no *t*-Bu-Gly-Lys (<0.05%). The procedure was repeated in the presence of Boc-Gly-OEt (50 equiv), an additional source of *tert*-butyl carbonium ion, during the deprotection step. Again, Lys (0.08%), Gly-Lys (100%), and no *t*-Bu-Gly-Lys (<0.05%) were detected. It was concluded that significant N-alkylation during the acidolytic cleavage of *tert*-butyloxycarbonyl peptides does not occur.

The possible occurrence of N-benzylation during solid phase peptide synthesis was then investigated. A portion of Boc-Gly-resin was treated with 50% TFA–CH_2Cl_2 containing 40 equiv of benzyl carbamate (Z-NH_2) for 1 h. The resin was washed, dried, and hydrolyzed in HCl–propionic acid.[14] No *N*-Bzl-Gly[15] (<0.1%) was detected. The occurrence of N$^{\epsilon}$-benzylation was indicated, however, when the cleavage mixture obtained from VIII was examined in more detail. Since Gly-Lys(Bzl) was not eluted on the ion-exchange system used to detect IX and X, a portion of the cleavage mixture was hydrolyzed in HCl–propionic acid[14] and then chromatographed on the short column of the amino acid analyzer at pH 7.0. A broad peak that eluted later than the basic amino acids was observed. An authentic sample of N^{ϵ}-Bzl-Lys[16] eluted at the same position, thereby indicating the presence of Gly-Lys(Bzl) (0.17%) in the cleavage mixture.

Portions of Boc-Lys(Z)-resin (VII) were treated with cleavage reagents containing TFA–CH_2Cl_2, HBr–HOAc–TFA,[17] and HF.[18] The results are given in Table I. Increasing concentrations of trifluoroacetic acid promoted increased formation of N^{ϵ}-Bzl-Lys. The addition of various carbonium ion scavengers to cleavage solutions containing trifluoroacetic acid did not significantly alter the formation of N^{ϵ}-Bzl-Lys from VII (Table II). The use of methanesulfonic acid–trifluoroacetic acid solutions[20] lowered the effect somewhat while

Table II. Reaction of Boc-Lys(Z)-R[a] with Cleavage Reagents Containing Carbonium Ion Scavengers

Run	Reagent	N^{ϵ}-Bzl-Lys, mol %
1	TFA–CH_2Cl_2 (1:1)	0.57
2	TFA–CH_2Cl_2 (1:1); 0.08 M DTT	0.88
3	TFA–CH_2Cl_2–anisole (5:4:1)	0.69
4	TFA–anisole (1:1)	0.40
5	TFA–*m*-xylene (1:1)	0.57
6	0.06 M MSA in CH_2Cl_2	0.47
7	0.06 M MSA in CH_2Cl_2–anisole (9:1)	0.24
8	0.01 M MSA and 0.1 M CF_3COOH in *m*-xylene	0.16
9	1 N HCl in glacial CH_3COOH	0.1
10	4 N HCl in dioxane	0

[a] See footnotes *a–c* of Table I for the materials and conditions used. The reactions were run for 14 h at room temperature and the resin products were cleaved with 16% HBr in TFA–HOAc (1:1). MSA, methanesulfonic acid; DTT, dithiothreitol. Limit of detection was 0.1 mol %.

hydrogen chloride in glacial acetic acid or dioxane depressed the formation of N^{ϵ}-Bzl-Lys to about the level of detectability.

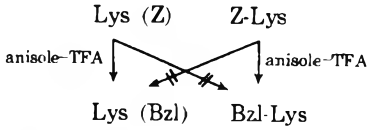
The formation of N^{ϵ}-benzyllysine from N^{ϵ}-benzyloxycarbonyllysine residues during deprotection by acidic reagents is a novel side reaction. It should be noted, however, that it is not the major side reaction that occurs during the deprotection of N^{α}-amino protecting groups in solid phase peptide synthesis. The major side reaction is the N^{ϵ}-decarbobenzoxylation of lysine side chains.[21-23] A calculation using the rate constant (1.9×10^{-6} s^{-1}) obtained for the N^{ϵ}-deprotection of Boc-[Lys(Z)]$_{10}$-Val-resin in 50% TFA–CH_2Cl_2[23] indicates that 9.1% cleavage of N^{ϵ}-benzyloxycarbonyl groups can be expected in 14 h. When VII was treated in 50% TFA–CH_2Cl_2 for 14 h the formation of 0.57% of N^{ϵ}-Bzl-Lys was observed (run 1, Table II). Therefore, about 6.5% of the prematurely N^{ϵ}-decarbobenzoxylated groups gave rise to N^{ϵ}-benzyl side chains. Both of these side reactions are dependent on the concentration of acid present in the deprotection reagent (runs 1–3, Table I) and on the acid stability of the Z group. The use of more acid-stable N^{ϵ}-protecting groups[21-23] has been shown to suppress the undesired deprotection reaction to acceptable levels and was expected to similarly suppress the N-alkylation reaction under the conditions of solid phase peptide synthesis. When Lys(2,4-Cl_2Z)[23] was allowed to stand in 50% TFA–CH_2Cl_2 for 67 h at room temperature only Lys (1.5%) and Lys(2,4-Cl_2Z) (98.5%) were detected. Since very little deprotection occurred, no Lys(2,4-Cl_2Bzl) (<0.1%) could be detected.

The above studies of N-benzylation dealt with the formation of *N*-benzyl amino acids and peptides during conditions which gave only partial deprotection of N^{ϵ}-Z groups. The occurrence of N-benzylation during conditions which allow complete decarbobenzoxylation, namely refluxing in anhydrous trifluoroacetic acid or treatment with CF_3SO_3H–TFA at 25 °C, was next investigated. The use of refluxing TFA for removal of Z groups was originally proposed by Weygand and Steglich[11] and it has found use in peptide synthesis,[24] although cleavage by anhydrous HBr remains by far the most frequently used method for acidolytic decarbobenzoxylations.[25] Samples of N^{α}-Z-Gly and N^{ϵ}-Z-Lys were refluxed in anhydrous TFA (30 min) and analyzed for the presence of free amino acid and *N*-benzyl amino acid. Anisole (20%) was present in a duplicate series of experiments. The results are given in Table III. Lower substrate concentrations reduced but did not entirely suppress N-benzylation in refluxing TFA. The presence of anisole also reduced but did not eliminate N-benzylation in refluxing TFA. When Lys(2,4-Cl_2Z) was refluxed in TFA for 10 h, the presence of Lys (96.2%), Lys(2,4-Cl_2Z) (1.0%), and Lys(2,4-Cl_2Bzl) (2.8%) was observed. In addition, treatment of N^{ϵ}-Z-Lys in refluxing TFA gave Lys and N^{ϵ}-Bzl-Lys; the formation of N^{α}-Bzl-Lys was not observed. Conversely, when N^{α}-Z-Lys was refluxed in TFA no formation of N^{ϵ}-Bzl-Lys was observed. These observations

Table III. N-Alkylation under Conditions of Complete Deprotection of Z-Gly and N^{ϵ}-Z-Lys in Refluxing TFA

Derivative	Concn, M	*N*-Benzyl amino acid,[a] mol %
Z-Gly	1.0	2.10 (0.98)[b]
Z-Gly	0.1	1.12 (0.49)
Z-Gly	0.01	0.96 (0.47)
N^{ϵ}-Z-Lys	0.1	3.26 (2.11)

[a] Z-Gly deprotects to give Gly and N^{α}-Bzl-Gly, while N^{ϵ}-Z-Lys gives Lys and N^{ϵ}-Bzl-Lys. Recoveries of 95–101% were observed. [b] The values in parentheses were obtained from duplicate runs in refluxing TFA containing 20% anisole.



suggest that the formation of *N*-benzyl groups from *N*-benzyloxycarbonyl groups in TFA may proceed via an intramolecular rather than intermolecular pathway.

The test system was also used to evaluate trifluoromethanesulfonic acid, a reagent that was recently proposed for the removal of protecting groups from amino acids and peptides.[26] Trifluoromethanesulfonic acid in methylene chloride or trifluoroacetic acid was reported to resemble HF[18] and boron tris(trifluoroacetate)[27] in its efficiency in cleaving protecting groups from amino acids and peptides. Trifluoromethanesulfonic acid (8.3–9.4 equiv) was added to 0.1 M solutions of Z-Gly and N^{ϵ}-Z-Lys in trifluoroacetic acid containing anisole (2.3–2.6 equiv). Samples were withdrawn at 30 min, quenched with aqueous buffer, and chromatographed on an amino acid analyzer. Z-Gly gave 1.22% of *N*-Bzl-Gly while N^{ϵ}-Z-Lys afforded 3.13% of N^{ϵ}-Bzl-Lys. Therefore, treatment by either trifluoromethanesulfonic–trifluoroacetic acid or refluxing trifluoroacetic acid (Table III) gave rise to N-benzylation during the decarbobenzoxylation of Z-protected amino acids. Pending further investigation, trifluoromethanesulfonic acid cannot be recommended as a general reagent (in lieu of HF, for example) for the removal of Z groups from peptides, although this reagent may prove to be advantageous in selected cases. In contrast, less than 0.1% N-alkylation was observed when Z-Gly, Lys(Z), and Lys(2,4-Cl_2Z) were treated with anhydrous HF (30–60 min, 25 °C). The best way to avoid N-benzylation is to use a substituted Z group which is stable during the multiple deprotections by TFA in a stepwise synthesis but can be removed by HF under conditions which do not cause N-benzylation.

It should be noted that the present investigation dealt with the Boc and Z protecting groups. The possible occurrence of N-alkylation reactions with other urethane-type protecting groups such as *p*-methoxybenzyloxycarbonyl,[28] biphenylisopropyloxycarbonyl,[4,5] and phenylisopropyloxycarbonyl[29] should be of interest to investigators using those protecting groups in peptide synthesis.

In summary, N^{ϵ}-*tert*-butylation was not observed when the Boc protecting group was used in model experiments employing the conditions of solid phase peptide synthesis. A novel side reaction, N-benzylation, was observed when Z groups were removed from Z derivatives of Gly and Lys by trifluoroacetic acid or trifluoromethanesulfonic–trifluoro-

acetic acid. This side reaction was not observed when a more acid-stable Z protecting group was used for lysine.

Experimental Section

Infrared spectra were taken with a Perkin-Elmer Model 237B grating infrared spectrophotometer, using KBr pellets. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Amino acid and peptide analyses were performed on Beckman amino acid analyzers (Models 120B and 121). Elemental analyses were performed by Mr. S. T. Bella of the Microanalytical Laboratory, The Rockefeller University. The solvents used for thin layer chromatography (TLC) (precoated 0.25-mm silica gel G plates, Analtech) were 1-butanol–acetic acid–water (BAW) (4:1:1), 1-butanol–acetic acid–water–pyridine (BAWP) (15:10:3:12), chloroform–methanol–acetic acid (CMA) (17:2:1), and chloroform–methanol–15% aqueous NH_3 (CMN) (4:5:2). Spots were visualized by spraying with 0.2% ninhydrin in 1-butanol and heating. The plates were then exposed to chlorine and sprayed with the o-tolidine reagent.

Z-Gly (Eastman) was twice recrystallized from chloroform while ϵ-Z-Lys (Schwarz Bioresearch) was used without further purification. Boc-Lys(Z) was obtained from Fox Chemical Co., and the unsubstituted resin support, a copolymer of styrene–1%-divinylbenzene (200–400 mesh), was purchased from Bio-Rad. The materials and methods for solid phase synthesis were similar to those described elsewhere[13,23,30] but modified as indicated.

N^{α}-Bzl-Gly·HCl. A modification of the method described by Greco et al.[31] for the general preparation of *N*-(substituted benzyl)glycine derivatives was used. Ethyl bromoacetate (11.3 ml, 100 mmol) was cautiously added to a solution of benzylamine (21.8 ml, 200 mmol) in benzene (70 ml). An immediate precipitation of benzylamine hydrobromide occurred. The suspension was refluxed (5 h), cooled, and filtered. The filtrate was evaporated in vacuo yielding a clear, mobile oil (22.1 g) which was refluxed in 6 N HCl (200 ml) for 1.5 h. The resulting solution was evaporated in vacuo until white crystals appeared. The suspension was allowed to stand in the cold for several hours. The crystals were collected, washed with diethyl ether, and dried to give 10.6 g of material, mp 220–225 °C (lit.[32] mp 220 °C). A minor contaminant was detected by TLC (BAWP). A recrystallization was effected from ethanol–diethyl ether, yielding first (5.97 g, mp 223–228 °C) and second (2.58 g, mp 223–226 °C) crops (42% yield) that were homogeneous by TLC, R_f 0.56 (BAWP).

N^{ϵ}-Bzl-Lys·HCl. Catalytic hydrogenation of N^{ϵ}-benzylidene-L-lysine[33] gave rise to the desired product, R_f 0.63 (CMN), in addition to a closely running contaminant, R_f 0.57. Attempts to free the product of the impurity were unsuccessful. The multistep synthesis of N^{ϵ}-benzyl-L-lysine hydrochloride, as described by Benoiton,[16] afforded material that was homogeneous by TLC and ion-exchange chromatography.

N^{α}-Z-N^{ϵ}-(2,4-Cl_2Bzl)-Lys. 2,4-Dichlorobenzaldehyde (1.75 g, 10.0 mmol) and ethanol (5 ml) were added to a solution of N^{α}-carbobenzoxy-L-lysine[33] in 1 N sodium hydroxide (10 ml). The solution was stirred at room temperature for 20 min and then cooled in an ice bath. Sodium borohydride (0.115 g, 3.00 mmol) was added in five portions over a 30-min period. After 15 min, the treatment with 2,4-dichlorobenzaldehyde and sodium borohydride was repeated and the solution was allowed to stir for 4 h. Water (15 ml) was added and the solution was extracted twice with diethyl ether (20 ml). A white solid was obtained when the solution was acidified (HCl) to pH 6.0 and cooled. The solid was collected and recrystallized from methanol–ethyl acetate, yielding 2.24 g (51%) of product: mp 168–170 °C; R_f 0.87 (CMN); $[\alpha]^{24}D$ +1.7° (*c* 2, acetic acid).

Anal. Calcd for $C_{21}H_{24}O_4N_2Cl_2$: C, 57.40; H, 5.50; N, 6.30; Cl, 16.14. Found: C, 57.46; H, 5.49; N, 6.39; Cl, 15.97.

Gly-Lys(Z). This compound was prepared from N^{α}-chloroacetyl-N^{ϵ}-benzyloxycarbonyl-L-lysine and ammonium hydroxide as described by Rao et al.,[10] R_f 0.32 (BAW).

***t*-Bu-Gly-Lyz(Z).** N^{α}-Chloroacetyl-N^{ϵ}-benzyloxycarbonyl-L-lysine[10] (0.933 g, 2.62 mmol) was refluxed in *tert*-butylamine (15 ml, 42 mmol) for 5 h. The *tert*-butylamine was removed in vacuo and the resulting foam was triturated with acetone to give solid material (0.720 g), mp 179–183 °C. Crystallization from methanol–ethyl acetate gave a white solid (0.332 g, 32% yield): mp 196–197 °C; R_f 0.35 (BAW); $[\alpha]^{25}D$ +7.2° (c 2, methanol). Carbonyl absorptions were observed in the infrared spectrum at 1686, 1596, and 1530 cm^{-1} and an absorption for *tert*-butyl was observed at 1254 cm^{-1}.

Anal. Calcd for $C_{20}H_{31}N_3O_5$: C, 61.05; H, 7.94; N, 10.68. Found: C, 60.86; H, 7.93; N, 10.68.

A sample of this material was examined by chemical ionization mass spectrometry.[34] The source temperature was 190 °C and the probe temperature approximately 125 °C. Major ions observed were *m/e* 394 (M + 1), 286 ($M^{\cdot+}$ − OCH_2Ph), 147, 91 ($PhCH_2^+$), and 74.

Analyses. Ion-Exchange Chromatography. Ion-exchange chromatography was performed using a Beckman amino acid analyzer (Model 120B or 121) at a flow rate of 66 ml/h and temperature of 56 °C. N^{α}-Bzl-Gly elutes exactly with phenylalanine on the long column (0.9 × 60 cm; AA-15 sulfonated polystyrene) of the analyzer.[15] The ninhydrin color yield of N^{α}-Bzl-Gly is 0.82 relative to Gly. N^{ϵ}-Bzl-Lys emerges from the short column (0.9 × 7 cm; PA-35 sulfonated polystyrene) at 161 min with pH 7.0 sodium citrate buffer. The ninhydrin color yield is 0.70 relative to Lys (28 min).

Samples of Gly-Lys(Z) and *t*-Bu-Gly-Lys(Z) were deprotected in refluxing TFA for 30 min.[11] The TFA was removed in vacuo and the resulting Gly-Lys and *t*-Bu-Gly-Lys trifluoroacetates were used to derive a chromatographic system capable of resolving NH_4Cl, Lys, Gly-Lys, and *t*-Bu-Gly-Lys. These compounds are resolved on the 0.9 × 60 cm column with pH 5.26 buffer.

Compd	Elution time, min	Ninhydrin color yield
Lys	193	1.00
Gly-Lys	235	1.28
NH_4Cl	297	1.29
t-Bu-Gly-Lys	346	0.43

A sample of N^{α}-Z-N^{ϵ}-(2,4-Cl_2Bzl)-L-Lys was decarbobenzoxylated with 32% hydrogen bromide in acetic acid. The HBr and acetic acid were removed in vacuo and the resulting Lys(2,4-Cl_2Bzl)hydrobromide was dissolved in a calibration solution containing Lys and Lys(2,4-Cl_2Z).[23] Lys(2,4-Cl_2Bzl) could not be eluted from the short column (0.9 × 7 cm) of the amino acid analyzer with pH 7 citrate buffer at elevated temperatures (56–90 °C) although Lys and Lys(2,4-Cl_2Z) are readily chromatographed under these conditions.[23] A column of Dowex 50W-X4 sulfonated polystyrene (0.9 × 9 cm), eluted (66 ml/h) with pyridine acetate buffer (0.8 M, pH 5.2) at 25 °C, allowed the resolution of Lys (23 min), Lys(2,4-Cl_2Z) (58 min), and Lys(2,4-Cl_2Bzl) (135 min).

Boc-Lys(Z)-resin.[35] Copoly(styrene–1% divinylbenzene) beads (Bio-Beads SX-1, 200–400 mesh) were washed, chloromethylated (1.0 mmol Cl/g), and brominated as described by Merrifield.[19] The cesium salt of Boc-Lys(Z) was prepared and allowed to react with the ring-brominated chloromethyl resin according to Gisin.[36] A picrate titration[9] after the removal of the Boc group (50% TFA–CH_2Cl_2) indicated a loading of 0.457 mmol Lys/g.

Boc-Gly-Lys(Z)-resin. Formation of *t*-Bu-Gly-Lys. Boc-Lys(Z)-resin (0.200 g, 0.0914 mmol) was placed in a 5-ml reaction vessel[30] and deprotected (30 min) with 50% TFA–$MeCl_2$. The resin was filtered, washed with CH_2Cl_2, and coupled with 10 equiv of Boc-Gly and 10 equiv of DCC in 4 ml of CH_2Cl_2. The coupling mixture was shaken (30 min), filtered, and washed with CH_2Cl_2.

The dipeptide resin was deprotected with 50% TFA–CH_2Cl_2 (30 min), filtered, washed with CH_2Cl_2, neutralized with 5% DIEA in CH_2Cl_2, and washed with CH_2Cl_2. The resin was shaken (30 min) with a cleavage solution containing 2 ml of TFA and 2 ml of 32% HBr in acetic acid.[17] The cleavage solution was filtered and the resin was washed with TFA, TFA–CH_2Cl_2 (1:1), and CH_2Cl_2. The pooled filtrates were evaporated in vacuo. The resulting residue was dissolved in water and subjected to ion-exchange chromatography. Analysis of the cleavage products gave Lys (0.16%), Gly-Lys (99.8%), and no *t*-Bu-Gly-Lys (<0.05%).

The above procedure was repeated with one variation: the Boc-Gly-Lys(Z)-resin was deprotected with 50% TFA–CH_2Cl_2 containing Boc-OEt (50 equiv). Chromatography of the cleavage products gave Lys (0.08%), Gly-Lys (99.9%), and no *t*-Bu-Gly-Lys (<0.05%).

Reaction of Boc-Lys(Z)-resin with Cleavage Reagents. Formation of N^{ϵ}-Bzl-Lys. A. Reaction with TFA–CH_2Cl_2. Solutions (2–4 ml) containing 5% TFA–CH_2Cl_2, 50% TFA–CH_2Cl_2, and 100% TFA were shaken with samples of Boc-Lys(Z)-resin (0.100–0.200 g) for 14 h at room temperature. The resins were filtered, washed with CH_2Cl_2, dried, and hydrolyzed in sealed ignition tubes containing HCl–propionic acid (1:1) for 6 h at 130 °C.[14] The analyses are given in Table I (runs 1–3).

B. Reaction with TFA–HBr–HOAc and HF. Untreated Boc-Lys(Z)-resin (0.100 g) was cleaved with TFA–32% HBr in HOAc (1:1) (1 h) and worked up as described for the TFA–HBr–HOAc cleavage of Boc-Gly-Lys(Z)-resin. Untreated Boc-Lys(Z)-resin (0.100 g) was also cleaved with anhydrous HF, in the absence of anisole, for 1 h at room temperature. The HF was removed in vacuo and the resin was

extracted with 1% HOAc. The use of either TFA–HBr–HOAc or HF did not allow formation (<0.1%) of N^{ϵ}-Bzl-Lys (runs 4 and 5, Table I).

C. Reaction with Cleavage Reagents Containing Carbonium Ion Scavengers. Solutions (2–4 ml) having the compositions listed in Table II were shaken with samples of Boc-Lys(Z)-resin (0.100–0.200 g) for 14 h at room temperature. The resins were filtered, washed with CH_2Cl_2, and cleaved with TFA–32% HBr in HOAc (1:1) as described above. The results are given in Table II.

Deprotection of Z-Gly and Lys(Z) in Refluxing Trifluoroacetic Acid. Solutions of Z-Gly (0.01, 0.10, 1.0 M) and Lys(Z) (0.1 M) in anhydrous TFA were prepared. Duplicate solutions containing 20% anisole were also prepared. The solutions were refluxed for 30 min and then evaporated in vacuo. The resulting residues were taken up in water and extracted twice with CH_2Cl_2. The aqueous solutions were analyzed for amino acid and *N*-benzylamino acid. Recoveries of 95–101% were observed. The results are given in Table III.

Deprotection of Z-Lys in Refluxing Trifluoroacetic Acid. A solution of Z-Lys[33] (1.0 M) was refluxed (30 min) in TFA and worked up as described above. No N^{ϵ}-Bzl-Lys (<0.1%) was detected. The presence of N^{α}-Bzl-Lys (0.6%) was established when a reference sample of N^{α}-Bzl-Lys, prepared by treating Bzl-Lys(Z)[37] with 32% HBr in HOAc, was chromatographed on the short column of the analyzer.

Deprotection of Z-Gly and Lys(Z) in Trifluoromethanesulfonic Acid–Trifluoroacetic Acid. Trifluoromethanesulfonic acid (8.3 equiv) was added to a solution of Z-Gly (0.1 M) in TFA containing anisole (2.3 equiv) with the immediate formation of a purple solution. An aliquot was removed at 30 min, quenched in pH 4.25 buffer, and analyzed. It contained N^{α}-Bzl-Gly (1.2%) and Gly (98.8%).

The experiment was repeated using Lys(Z) (0.1 M) in TFA containing anisole (2.6 equiv) and trifluoromethanesulfonic acid (9.4 equiv). At 30 min an aliquot was removed, quenched in pH 7.00 buffer, and analyzed. It contained N^{ϵ}-Bzl-Lys (3.1%) and Lys (96.9%).

Deprotection of Z-Gly and Lys(Z) in HF. Z-Gly (20.9 mg, 100 μmol) and Lys(Z) (28.0 mg, 100 μmol) were allowed to stir in anhydrous HF (5 ml) for 30 min at room temperature. The HF was removed in vacuo and the resultant residue was extracted with water. An insoluble, light yellow solid was filtered off and the filtrate was evaporated in vacuo, yielding a residue which was dissolved in water (12.5 ml) for ion-exchange chromatography. Neither N^{α}-Bzl-Gly nor N^{ϵ}-Bzl-Lys could be detected (<0.1%).

Deprotection of Lys(2,4-Cl_2Z) in HF. Lys(2,4-Cl_2Z) (70.4 mg, 202 μmol) was stirred in anhydrous HF (10 ml) for 1 h at room temperature. The HF was removed in vacuo and the resulting material was extracted with pyridine acetate buffer (0.8 M, pH 5.2). A white solid was removed by filtration and a portion of the filtrate was subjected to ion-exchange chromatography. Less than 0.1% Lys(2,4-Cl_2Bzl) was present.

Registry No.—N^{α}-Bzl-Gly·HCl, 7689-50-1; N^{ϵ}-Bzl-Lys·HCl, 38299-38-6; N^{α}-Z-N^{ϵ}-(2,4-Cl_2Bzl)-Lys, 58581-65-0; *t*-Bu-Gly-Lys(Z), 58581-66-1; N^{ϵ}-benzylidene-L-lysine, 14511-39-8; 2,4-dichlorobenzaldehyde, 874-42-0; N^{α}-carbobenzoxy-L-lysine, 2212-75-1; N^{α}-chloroacetyl-N^{ϵ}-benzyloxycarbonyl-L-lysine, 47376-73-8; *tert*-butylamine, 75-64-9; Z-Gly, 1138-80-3; N^{ϵ}-Z-Lys, 1155-64-2; Boc-Lys(Z)-H, 2389-60-8; Lys(2,4-Cl_2Z), 58581-67-2.

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Secondary Valence Force Catalysis. 16. Melittin-Catalyzed Hydrolysis of *p*-Nitrophenyl Dodecanoate

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Melittin, a cationic surface active polypeptide containing 26 amino acid residues isolated from the venom of the common honeybee *Apis mellifera*, is an effective catalyst for the hydrolysis of *p*-nitrophenyl dodecanoate. Catalytic activity reflects the capacity of melittin to (1) disperse aggregates of this ester which form in aqueous solution and (2) facilitate attack of hydroxide ion on the dispersed ester. An unexpected observation is the finding that a complex of dodecanoate and melittin is a more effective catalyst than is melittin itself. This is a unique example of the facilitation of the attack of an anionic nucleophile by an anionic surfactant.

The rates of many organic reactions are influenced by the nature and the concentration of micelle-forming amphipathic, or surfactant, molecules or ions.[1-5] Such molecules generally consist of a straight hydrocarbon chain, usually 8–18 carbon atoms in length, to which a polar head group is attached. In some cases the head group only provides a specific chemical environment for the reaction; in others it participates directly in the reaction as, for example, a nucleophile. The similarities between micelles and globular proteins and the utility of micelles in organic synthesis[6] have stimulated considerable interest in micelle-catalyzed reactions. Previous investigations have provided significant information concerning the principal features of reactions catalyzed by structurally simple surfactants. Consequently, it appears appropriate to deviate from established patterns in order to probe the possible catalytic properties of more complex surfactants, especially those which are polypeptides and, hence, which may shed new light on enzymatic reaction mechanisms.

One example of a complex polypeptide amphipath is the low molecular weight polypeptide, melittin,[7] which is the major component of venom obtained from the common honeybee, *Apis mellifera*. The primary structure is provided below:[8]

Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-
5 10

Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-Gln(NH_2)
15 20 25

A single melittin subunit consists of 26 amino acids. Since the two γ-carboxyl groups of residues 25 and 26 and the C terminus occur as the corresponding amides, there are no negatively charged centers. In contrast, there are six free basic groups: the N terminus, the lysine residue at position seven, and the sequence of four residues near the blocked C terminus. The amino acid sequence is worthy of note: predominantly hydrophobic residues occur in positions 21–26, and, as a consequence, melittin has amphipathic character analogous to that of simpler cationic surfactants. In aqueous solution melittin forms micellelike, highly surface-active[9] structures which contain four polypeptide molecules per aggregate.[10-12] Since cationic surfactants catalyze the hydrolysis of certain aliphatic esters,[13] we chose to probe the possible catalytic activity of melittin for the hydrolysis of *p*-nitrophenyl dodecanoate. The results are presented herein.

Experimental Section

Materials. *p*-Nitrophenyl dodecanoate[14] was prepared by a slight modification of the general procedure of Bender and Nakamura:[15] 0.125 mol of *p*-nitrophenol, 0.10 mol of dodecanoyl chloride, and 0.10 mol of pyridine were dissolved in 100 ml of toluene and refluxed for 1 h. The reaction mixture was then neutralized with saturated $NaHCO_3$ and washed consecutively with water, 5% NaOH, 0.1 N HCl, and finally with water. The resulting solution was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The ester, a light yellow, waxy solid, mp 40–41 °C (lit.[14] 46 °C), carbonyl stretching frequency (liquid film) at 1755 cm^{-1}, was not purified further.

Melittin was purified from the venom of the common honeybee (*Apis mellifera*).[12] One gram of the whole lyophilized crude venom, obtained from Sigma Chemical Co., was dissolved in 2 ml of a 0.1 M ammonium formate buffer, pH 4.5, and applied to a Sephadex G-50 column (1.1 × 300 cm) previously equilibrated with the ammonium formate buffer. The melittin-rich fractions were pooled and lyophilized. The brown powder thus obtained was dissolved in 15 ml of distilled water and divided into ten fractions. A saturated picric acid solution (1.5 ml) was added to each of the ten fractions causing the melittin to precipitate as the picrate complex. The precipitate was washed twice with a 70% picric acid solution and collected by centrifugation. The recovered picrate was dissolved in acetone and dissociated by the addition of concentrated HCl. The precipitation step was repeated and the protein was collected and washed twice with a 1% HCl–acetone solution. The melittin was dissolved in water, the pH was adjusted to 3.0 by the addition of HCl, and the solution was passed through a Dowex AG-1-X8 column (Cl^- form) (0.8 × 10 cm) in order to remove trace amounts of picric acid. The purified protein, 350–400 mg/g crude venom, was stored in aqueous solution at 4 °C.[16]

Other reagents were obtained commercially. Inorganic salts were used without further purification. Glass-distilled water was employed throughout.

Kinetic measurements were performed spectrophotometrically with the aid of a Zeiss PMQII spectrophotometer equipped with a thermostated cell holder. All measurements were made at 25 °C. Reactions were monitored at 400 nm, near the absorption maximum of the *p*-nitrophenolate anion. Each reaction mixture initially contained 3 × 10^{-2} M triethylamine–ammonium ion buffer. Measured quantities of solid *p*-nitrophenyl dodecanoate were dissolved in acetonitrile in such proportions that the addition of 20 μl of this solution to 3.0 ml of reaction mixture gave the desired ester concentration. First-order rate constants were calculated using the initial straight-line portions of plots of log ($OD_\infty - OD_t$) vs. time in the usual manner. Values of pH were measured with the aid of a Radiometer PHM4c pH meter equipped with a glass electrode.

Results

Hydrolysis of *p*-nitrophenyl dodecanoate at 25 °C and pH 10.0 in the presence of melittin was monitored by observing the appearance of the *p*-nitrophenolate anion. No reaction occurs in the absence of added polypeptide. In Figure 1, the data for this reaction in the presence of melittin are plotted in the usual manner for a pseudo-first-order reaction. It is obvious that the reaction does not obey simple first-order kinetics and that the rate of ester hydrolysis increases with increasing time. Using data from the initial straight-line portion of this curve, an approximate first-order rate constant of 0.056 min^{-1} can be calculated. If, on the other hand, one employs data taken near the terminus of the reaction, the corresponding rate constant is 0.21 min^{-1}.

Following completion of the hydrolysis of 3 × 10^{-5} M *p*-nitrophenyl dodecanoate in the presence of 1 × 10^{-4} M melittin, addition of a second aliquot of ester to give again an ester

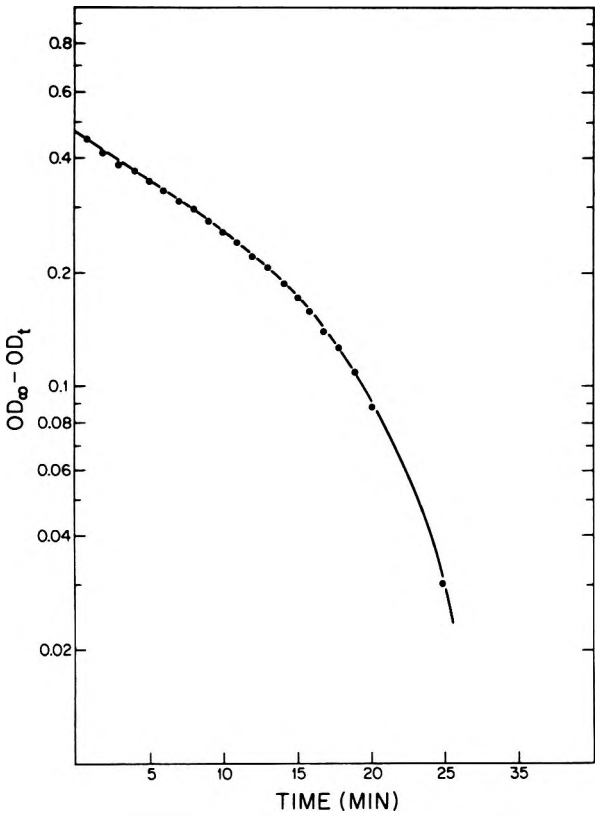

Figure 1. Data for the hydrolysis of 3×10^{-5} M *p*-nitrophenyl dodecanoate at pH 10.0 and 25 °C in the presence of 1×10^{-4} M melittin plotted according to the usual method for first-order reactions. Employing the data points near the beginning of the reaction yields a first-order rate constant of 0.056 min^{-1}.

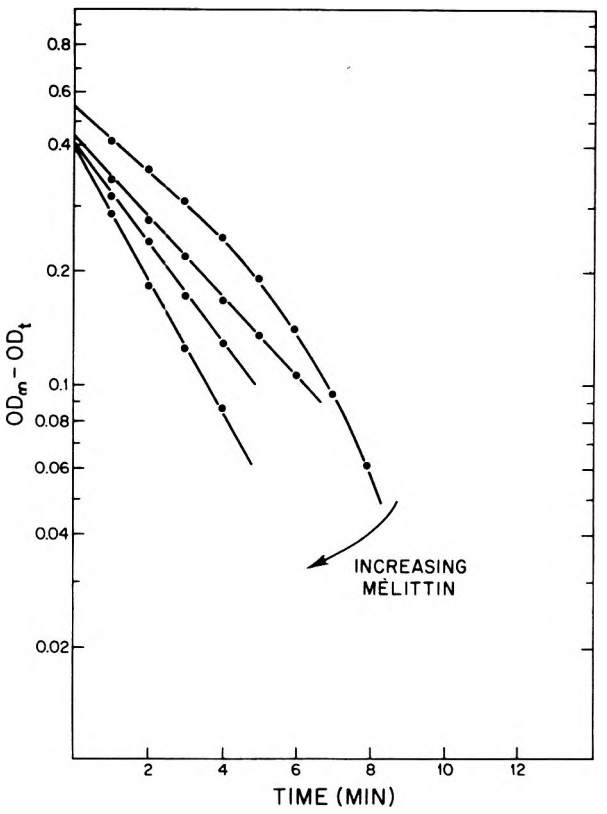

Figure 3. Data for the hydrolysis of 3×10^{-5} M *p*-nitrophenyl dodecanoate at pH 10.0 and 25 °C in the presence of various concentrations of melittin plotted in the usual manner for first-order reactions. The concentrations of melittin, in increasing amounts as indicated, are 2.5×10^{-4}, 5.0×10^{-4}, 7.5×10^{-4}, and 1.0×10^{-3} M.

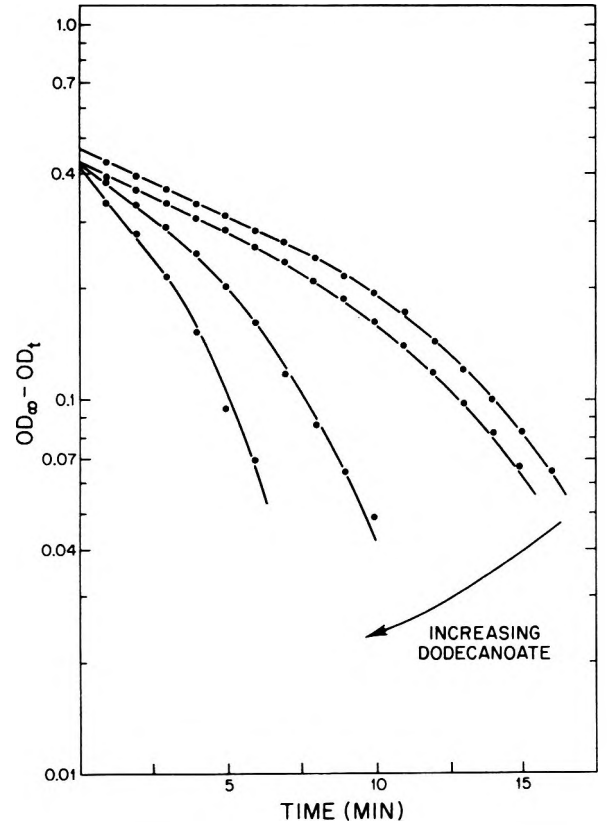

Figure 2. Data for the hydrolysis of *p*-nitrophenyl dodecanoate at pH 10.0 and 25 °C in the presence of 1×10^{-4} M melittin and varying concentrations of dodecanoate plotted according to the usual method for first-order reactions. The concentrations of dodecanoate, in increasing amounts as indicated, are 7.5×10^{-6}, 1.5×10^{-5}, 3.0×10^{-5}, and 4.5×10^{-5} M.

concentration of 3×10^{-5} M results in an initial rate of ester hydrolysis equal to the terminal rate observed for the first reaction. As before, the rate of ester hydrolysis increases with increasing time. These results establish that the melittin-dependent hydrolysis of *p*-nitrophenyl dodecanoate is autocatalytic.

The simplest explanation for this autocatalytic behavior is that one or both of the reaction products combine with melittin to form a more effective catalyst than melittin alone. In an effort to probe this possibility, measured quantities of dodecanoic acid were added to the reaction mixture prior to its initiation. In Figure 2 the time course plots for ester hydrolysis in the presence of four concentrations of added dodecanoate are shown. In each case, significant deviations from first-order kinetics are observed. Both initial and final rate constants increase regularly with increasing dodecanoate concentration. An approximately linear relationship is obtained between the initial first-order rate constants and dodecanoate concentration; the addition of 4.5×10^{-4} M dodecanoic acid increases the rate of reaction approximately threefold.

In the presence of higher melittin concentrations the reaction kinetics for the basic hydrolysis of *p*-nitrophenyl dodecanoate are simpler. In Figure 3, first-order plots for this reaction at melittin concentrations ranging from 2.5×10^{-4} to 1.0×10^{-3} M are shown. There is significant deviation from simple first-order kinetics only at the lowest melittin concentration employed. The respective rate constants for these reactions, evaluated from data near the beginning of the reaction for the lowest concentration of melittin for which deviations from first-order kinetics were observed, are plotted as a function of melittin concentration in Figure 4. Although some scatter in the data is evident, the rate constants increase regularly with increasing concentration of melittin. The

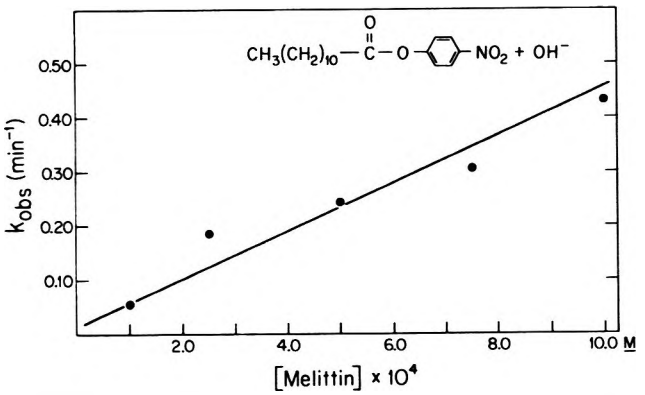

Figure 4. First-order rate constants for melittin-dependent hydrolysis of *p*-nitrophenyl dodecanoate at pH 10.0 and 25 °C plotted as a function of melittin concentration. For the lower concentration of melittin, the first-order rate constants were evaluated from data taken in the first half-life of the reaction only.

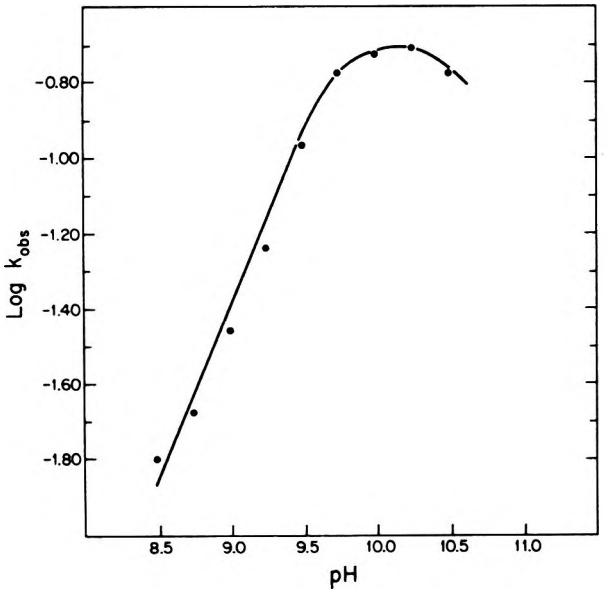

Figure 5. Logarithms of first-order rate constants for hydrolysis of 3×10^{-5} M *p*-nitrophenyl dodecanoate at pH 10.0 and 25 °C and in the presence of 2.5×10^{-4} M melittin plotted against pH.

maximal rate constant obtained, 0.434 min^{-1}, is approximately eightfold greater than that observed at the lowest melittin concentration employed.

In Figure 5, logarithms of first-order rate constants for hydrolysis of *p*-nitrophenyl dodecanoate catalyzed by 2.5×10^{-4} M melittin are plotted as a function of pH. At this concentration of melittin, ester hydrolysis yields a satisfactory approximation to first-order kinetics through at least 1 half-life; rate constants were calculated from data taken during the first half-life of the reactions. In the pH range in which rate constants increase with increasing hydroxide ion concentration, the slope of the line in this plot is somewhat less than unity. At higher values of pH, rate constants become relatively independent of this variable.

In Figure 6, first-order plots for the melittin-catalyzed hydrolysis of *p*-nitrophenyl dodecanoate at pH 10.0 in the presence of 1×10^{-4} M are shown for three concentrations of added sodium bromide. With increasing salt concentration, deviations from first-order kinetics become less noticeable and, moreover, the rate of ester hydrolysis decreases modestly. Similar behavior was observed for addition of sodium chloride and sodium nitrate, the former being less effective and the

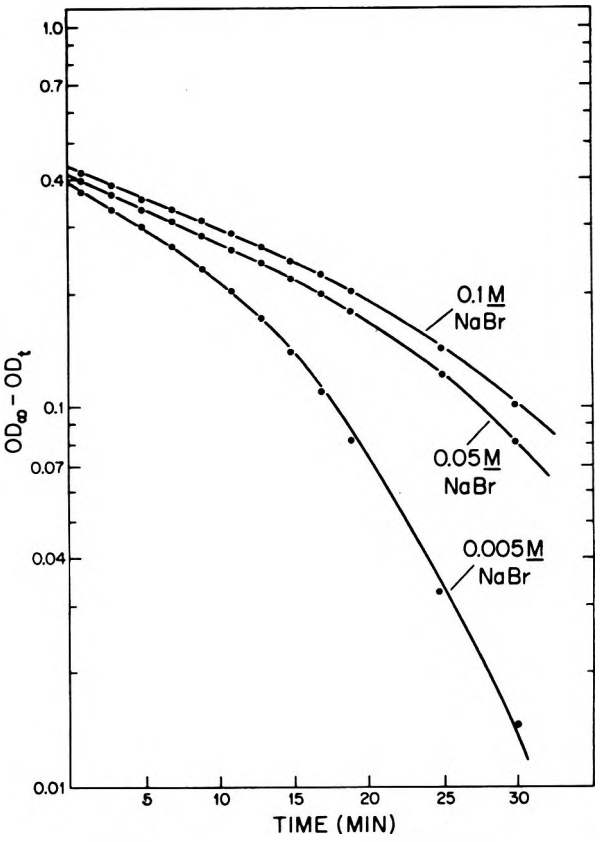

Figure 6. Data for hydrolysis of *p*-nitrophenyl dodecanoate at pH 10.0 and 25 °C and in the presence of 1×10^{-4} M melittin plotted according to the usual method for a first-order reaction at three concentrations of added sodium bromide.

latter more effective than sodium bromide in eliciting the indicated changes.

Discussion

Several features of the hydrolysis of *p*-nitrophenyl dodecanoate in aqueous solution have been probed in detail by Menger and Portnoy.[17] These workers have established that this ester forms aggregates in water; the individual molecules in such aggregates are extremely unreactive toward hydroxide ion. Reactivity is so low that no reliable second-order rate constants for attack of hydroxide ion on this substrate in water are available. Agents which disperse the *p*-nitrophenyl dodecanoate aggregates lead to greatly increased rates of base-catalyzed hydrolysis.[13,17]

Previous reports from this laboratory have established that simple *n*-alkyltrimethylammonium bromides are effective catalysts for the basic hydrolysis of *p*-nitrophenyl dodecanoate and structurally related esters.[13] Since rate constants for the hydrolysis of this ester in the presence of such surfactants are greater than those for hydrolysis of water-soluble esters of inherently equal reactivity, such as *p*-nitrophenyl hexanoate and acetate, in the absence of surfactants, it follows that factors other than dispersal of ester aggregates must intervene. The electrostatic field at the cationic micellar surface, which will have the effects of stabilizing the negatively charged transition state and of concentrating hydroxide ion at the micellar surface, must be responsible for a portion of the total catalytic effect.

The above considerations identify two catalytic mechanisms by which melittin may increase the rate of *p*-nitrophenyl dodecanoate hydrolysis: promotion of ester dispersal, with formation of ester–polypeptide aggregates, in the aqueous environment and electrostatic facilitation of the attack of hydroxide ion. In addition, it is possible that one or more of

the nucleophilic groups present in the melittin molecule may attack the ester substrate directly, increasing the rate of p-nitrophenolate liberation. That the rate of p-nitrophenyl dodecanoate hydrolysis is readily measureable at pH 10.0 in the presence of dilute solutions of melittin is proof that the first mechanism at least is operative. For example, the rate constant for ester hydrolysis at pH 10.0 in the presence of 1×10^{-4} M melittin, based on the data points early in the reaction, is 0.05 min^{-1}. This value is, coincidentally, almost the same as that measured for the hydrolysis of p-nitrophenyl hexanoate, an ester which does not aggregate, in the absence of melittin or surfactants at the same pH and temperature.[13] The observation that the first-order rate constants for ester hydrolysis increase about eightfold at higher concentrations of melittin (Figure 4) establishes that melittin facilitates ester hydrolysis by some mechanism other than ester dispersal. The magnitude of the catalytic effect is similar to that elicited by simple cationic surfactants and suggests that the electrostatic field present at the surface of the melittin micelle may underlie the catalytic effect. Were nucleophilic participation by basic groups on the melittin molecule involved, greater rate increases might have been expected.

One of the intriguing aspects of melittin-dependent p-nitrophenyl dodecanoate hydrolysis is the autocatalytic behavior observed at low melittin concentrations and the rate enhancement elicited by the addition of the anionic product of the reaction, dodecanoate. Previous work has shown that anionic surfactants alone inhibit base-catalyzed ester hydrolysis.[13] Consequently, the discovery that the addition of dodecanoate to melittin solutions, either through product accumulation or exogenous addition, produces increased rates for ester hydrolysis is unexpected and surprising. The results strongly suggest that a complex between dodecanoate and melittin is formed which is a better catalyst than melittin alone. In addition, the observation that higher melittin concentrations produce reactions which are kinetically first order requires that autocatalysis depends critically upon the ratio of the number of moles of melittin to the number of moles of dodecanoate. To the best of our knowledge, this is the only case in which an anionic reagent increases the capacity of a cationic reagent to catalyze an organic reaction.

Aside from ester dispersion, melittin catalysis for p-nitrophenyl dodecanoate decomposition may be viewed as either (1) electrostatic facilitation by cationic melittin of the attack of hydroxide ion on the ester substrate or (2) direct nucleophilic attack of melittin on the ester with formation of acylated melittin (at serine, threonine, or lysine). The fact that added dodecanoate elicits the same catalytic effect as is observed in the course of the reaction at low melittin concentrations is consistent with the former observation, since dodecanoate is a reaction product. In the latter case, however, dodecanoyl–melittin would be expected to be stable under the reaction conditions and the autocatalytic reaction would have to be ascribed to acylated melittin. The fact that added dodecanoate elicits the same rate effects would, then, have to be coincidental.

The complex pH–rate profile for melittin-catalyzed hydrolysis of p-nitrophenyl dodecanoate (Figure 5) is almost certainly the consequence of a combination of effects. The effect on reaction rate of increasing hydroxide ion concentration may be partially or completely offset by a decreasing positive charge on the melittin molecule reflecting neutralization of the cationic lysine residues. To the extent that the catalytic activity of melittin depends on its cationic character, catalysis will diminish with increasing pH.

Finally, added inorganic anions have two effects on the kinetics of the melittin-catalyzed hydrolysis of p-nitrophenyl dodecanoate. The first is to cause the reactions to become somewhat more nearly first order at low melittin concentrations, and the second is to cause a slight reduction in rate. The fact that the reactions approach first-order kinetics may reflect the decreased ability of melittin to bind dodecanoate in the presence of inorganic ions. Sites on the protein molecule which might have been previously available to carboxylate ions are instead occupied by added inorganic anions. The observation that rates of ester hydrolysis are somewhat slower may also be a result of binding inorganic anions to the melittin molecules. To the extent that the positive charges on the protein aggregates are neutralized via association with the inorganic anions, that component of the melittin catalysis which depends upon electrostatic stabilization will be diminished. Inorganic anions are known to be potent inhibitors of the cationic surfactant catalysis for ester hydrolysis.[13]

Acknowledgements. This work was supported by Research Grant GM 19631 from the National Institutes of Health. B.K.M was the recipient of an Ira E. Lee Scholarship, summer 1975.

Registry No.—Melittin, 20449-79-0; p-nitrophenyl dodecanoate, 1956-11-2.

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Pathway Control of Products in the Reaction of Nitrosyl Chloride on Oximes

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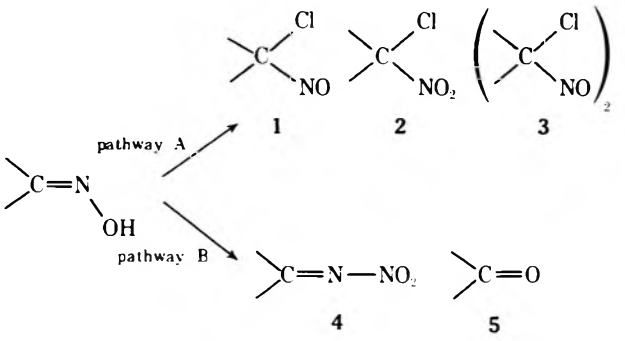
The two pathways of reaction of nitrosyl chloride with oximes were found to be sensitive to three parameters: polarity of solvent, concentration of nitrosyl chloride, and concentration of oxime. Pinacolone oxime, which takes both pathways, was examined with respect to each variable. The two pathways can be controlled over rather wide limits by variation in the three parameters. Pinacolone is produced directly from the oxime by a mechanism which cannot involve hydrolysis since water was excluded from the reaction with nitrosyl chloride. A pathway to account for the production of chloronitroso compound **1**, nitrimine **4**, and ketone **5** is given.

The ambident nature of nitrosyl chloride has been mentioned in a review[1] describing normal and anomalous reaction products in the nitrosochlorination of alkenes. Kadzyauskas and Zefirov point out that slight changes in conditions may produce substantial changes in the pathway of the reaction. We were impressed by the sensitivity of the reagent to changes in reaction conditions in repeating a reaction of nitrosyl chloride not with an alkene but with an oxime, first reported in 1927. Rheinboldt and Dewald[2] reported a 19% yield of the chloronitroso compound, type **1** (Scheme I), as the only

Scheme I



product from a 0.38 M solution of pinacolone oxime in ethyl ether when treated with liquid nitrosyl chloride. We obtained a 51% yield of pinacolone nitrimine, type **4**, from a 0.45 M solution of the same oxime in chloroform with gaseous nitrosyl chloride.[3]

Search of the literature[2-6] (Table I) suggested that many oximes react predominantly by pathway A (Scheme I) to incorporate chlorine; others appear only to react by pathway B; and a few gave products from both pathways (camphor oxime, pinacolone oxime). The results in Table I suggested enough anomalies that generalizations might be forthcoming from closer control over reaction conditions.

Preliminary experiments suggested that a systematic study of the sensitivity of the reagent to solvent polarity, concentration of the oxime, and concentration of the reagent would be worthwhile on an oxime that took both pathways. For this purpose pinacolone oxime was chosen over camphor oxime since it gave all five types of products, **1**–**5** (Scheme I), which could be conveniently identified.

Since **1** is the initial product in pathway A and subsequently precipitates as dimer (**3**) or is oxidized to **2**, the results obtained from a change of solvent polarity are reported in Figure 1 as a ratio of pathway A to pathway B where pathway A represents the total yield of (**1** + **2** + **3**). The yield by pathway B includes (**4** + **5**). The ratios are shown as a function of solvent polarity as measured by the dielectric constants for carbon tetrachloride, chloroform, methylene chloride, and the oxygen-containing solvents, ether and nitromethane. The ratio of products from pathway A to products from pathway B is greater as the dielectric constant increases but it is not a continuous function; oxygen solvents, ether and nitromethane, give an added tilt to the ratio. However, within these results is a hidden anomaly. The ratio of **4** to compound **5** was nearly 5 in carbon tetrachloride and nitromethane while the ratio is approximately 1 in the solvents of intermediate polarity (Table II).

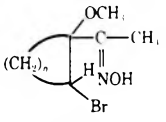
The distribution of products was also found to depend both on the concentration of oxime and concentration of nitrosyl chloride. Chloroform was chosen as solvent for this series of experiments using a molar ratio of 2:1 for nitrosyl chloride to oxime (Figure 2). As the concentration of oxime increased the formation of ketone **5** and nitrimine **4** increased at the expense of chloronitroso compound **1**. At low oxime concentration (up to 1 M), nitrimine and ketone are formed in about equal molar amounts but at a concentration of 2 M, the product mixture was noticeably richer in nitrimine (Table III).

To examine the effect of the molar ratio of nitrosyl chloride to oxime, different molar ratios were used on oxime solutions of the same concentration (1 M), again in chloroform at 25 °C. The results shown in Figure 3 suggest that at a molar ratio of nitrosyl chloride to oxime of 4, chloronitroso compound formation dominates but does not stifle formation of **4** completely. The ratio of nitrimine to ketone remains essentially one at all ratios of reagent to oxime at this concentration (Table IV and Figure 3).

The question of the origin of the ketone in this reaction is relevant since it is known that nitrimines and chloronitroso compounds[7] both hydrolyze to ketones as do oximes. However, water was excluded in the present work and we conclude that the ketone is a primary reaction product. To test this point the reaction of nitrosyl chloride with pinacolone oxime was monitored at intervals to see if the percentage of nitrimine or chloronitroso compound diminished as the reaction progressed. This reaction was carried out at a low molar ratio of reagent to oxime to ensure that nitrimine and ketone were the dominant products. Table V gives the product distribution at approximately one-fourth (29%), half (54%), three-fourths (77%), and completion (100%) of the reaction. Each of the three products **1**, **4**, and **5** increased steadily in amount. There was no decrease in **1** or **4** in any interval. While this does not exclude some formation of ketone from a secondary process it strongly suggests that ketone is mainly formed directly by the reagent. Stirring the reaction mixture with nitrosyl chloride present for 5 h after completion of the reaction also did not change the final product distribution.

When pinacolone oxime was allowed to react with nitrosyl chloride under radiation by an ultraviolet lamp or in the presence of free-radical inhibitors (iodine and hydroquinone) no induction period or change in product distribution was observed.

Table I. Reaction Products of Oximes with Nitrosyl Chloride

Oxime	Pathway A Chloronitroso, %	Pathway B Nitrimine, %	Pathway B Ketone, %
Acetaldehyde	7.4[a]		
α,β-Dibromodihydrocinnamaldehyde	*b*	94[c]	
Diethyl ketone	36[d]		
Ethyl *n*-propyl ketone	48[e]		
Dibenzyl ketone	70[e]		
Cyclohexanone	60[e]		
α-*tert*-Butylcyclohexanone		92[f]	
Methyl 1-chlorocyclohexyl ketone		64[g]	
Methyl 1-chlorocyclopentyl ketone		55[g]	
Benzophenone		20[e]	31,[e] 84[c]
p-Methoxybenzophenone, syn		*h*	*h*
p-Methoxybenzophenone, anti		*h*	*h*
1,3-Diphenyl-2,3-dibromopropanone	*c, i, j*	70[c]	
1-*p*-Methoxyphenyl-1,2-dibromo-3-butanone		*i, k*	
p-Nitrobenzophenone	*h* (chloronitro)	*h*	
Camphor	18	24	
Pinacolone	19[e]	51[f]	
		77[l] (*n* = 3) 89[l] (*n* = 4)	

[a] Reference 2; yields of chloronitroso compound not given on ten other aliphatic aldehydes. [b] 12% yield of 1,3-dichloro-2-bromo-1-nitroso-1-phenylpropane (dimer) and 83% yield of α,β-dibromodihydrocinnamhydroxamic chloride, ref 5. [c] Sealed tube, excess nitrosyl chloride. [d] Reference 2; yields of nitrimines not given on 12 other aliphatic ketones. [e] Reference 2. [f] Reference. 3. [g] Reference 6. [h] Reference 2; yields not given. [i] Reference 5. [j] 26% yield of 1-chloro-1-nitro-1,3-diphenylpropene. [k] 46% yield of 1-*p*-methoxy-1-chloro-2-bromo-3-butanonenitrimine. [l] Reference 4.

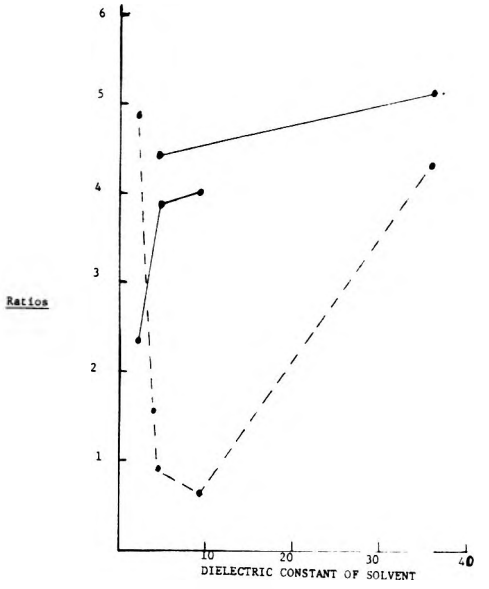


Figure 1. Reaction of nitrosyl chloride with pinacolone oxime (1.43 M) as a function of solvent polarity at 25 °C, [NOCl]/[oxime] = 3. Data from Table II: a, solid line, ratio of product yields of pathway A to pathway B; b, broken line, ratio of nitrimine, 4 to ketone, 5 as a function of dielectric constant of various solvents.

Table II. Products in the Reaction of Nitrosyl Chloride with Pinacolone Oxime (1.43 M) and [NOCl]/[Oxime] = 3 at 25 °C as a Function of Solvent Polarity

Solvent	CCl_4	$CHCl_3$	CH_2Cl_2	$(C_2H_5)_2O$	CH_3NO_2
Dielectric const, ε	2.24	4.81	9.08	4.34	35.8
Pathway A (1 + 2 + 3, %)	70.1	79.6	80.1	81.8	83.7
Pathway B % nitrimine, 4	24.8	9.5	7.8	11.0	13.1
% ketone, 5	5.1	10.9	12.1	7.2	3.2
Pathway A / Pathway B	2.3	3.9	4.0	4.5	5.1
Nitrimine / Ketone	4.9	0.9	0.65	1.5	4.3

Table III. Products in the Reaction of Nitrosyl Chloride with Pinacolone Oxime as a Function of Oxime Concentration in Chloroform at 25 °C with [NOCl]/[Oxime] = 2.0

[Oxime]	0.25 M	0.5 M	1.0 M	2.0 M
% chloronitroso, (1 + 2 + 3)	92.0	78.8	72.7	45.8
% nitrimine, 4	3.5	8.8	14.7	37.1
% ketone, 5	4.5	12.4	12.6	17.1

The results can be rationalized in terms of the polar mechanism proposed by Freeman[8] where the key intermediate is a nitrosonitrone 6 (Scheme II). We add a second molecule of nitrosyl chloride in a pseudo-six-membered ring to account for pathway A predominating to give chloronitroso product with an excess of the reagent. In polar solvents and excess nitrosyl chloride (also strongly polar) ionization to give chloride ion in the pseudo-six-membered ring would be promoted. In less polar solvents and in very low concentrations of reagent the nitrone oxygen competes favorably as a nucleophile with chlorine to give the products of pathway B, ketone and nitrimine. Apparently the methyl and *tert*-butyl groups give the right electronic and steric requirements when pathway B predominates to allow approximately equal probabilities for the two three-membered ring intermediates 7 and 8. The pathway to ketone was shown to include intermediate 7 by Wieland and Grimm[9] with oxygen labeling as shown in Scheme II which resulted in 89% of the label in the nitrous oxide. Freeman[10] has raised objections to the three-membered ring being the only pathway to ketone but it does seem to be the simplest explanation of the results in the absence of water.

A referee suggested that compound 1 could be formed in a

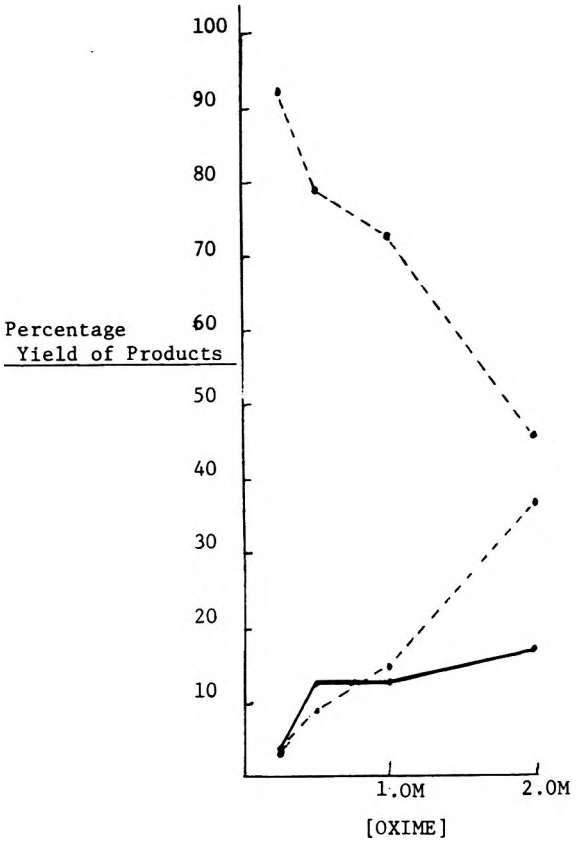
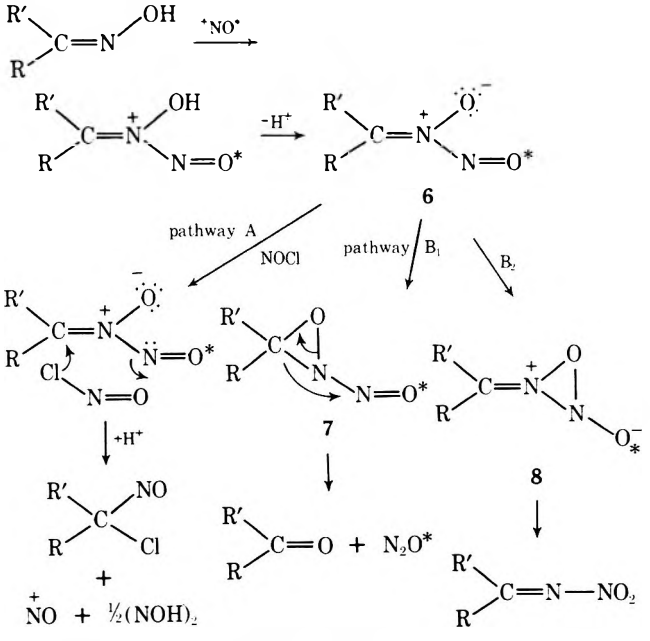
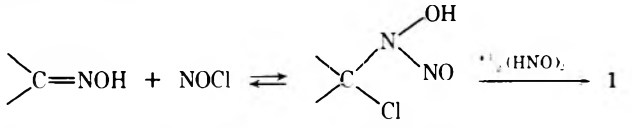


Figure 2. Reaction of nitrosyl chloride with pinacolone oxime as a function of oxime concentration in chloroform at 25 °C, [NOCl]/[oxime] = 2.0. Data from Table III: a, upper broken line, percent chloronitroso product, 1; b, lower broken line, percent nitrimine, 4; c, solid line, percent ketone, 5.

Scheme II



by-pass of **6** with high ratios of nitrosyl chloride to oxime in the following way:



However, the reversible formation of the relatively less polar adduct should not be sensitive to changes in the polarity of solvent, contrary to the findings in this work (Table II and Figure 1). Instead in pathway A, more polar solvents should stabilize our suggested intermediate (Scheme I) and promote ionization of nitrosyl chloride in the pseudo-six-membered ring as was found.

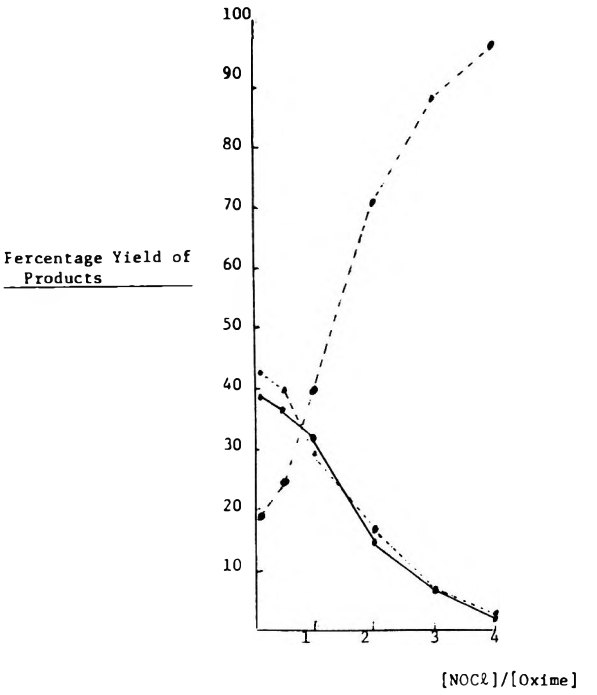


Figure 3. Reaction of nitrosyl chloride with pinacolone oxime as a function of [NOCl]/[oxime] in chloroform at 25 °C, [oxime] = 1.0 M at start. Data from Table IV: a, upper broken line, percent chloronitroso product, 1; b, solid line, nitrimine, 4; c, lower broken line, ketone, 5.

Table IV. Products in the Reaction of Nitrosyl Chloride with Pinacolone Oxime at a Starting Concentration (1 M) in Chloroform at 25 °C as a Function of [NOCl]/[Oxime]

[NOCl]/[Oxime]	0.1	0.5	1.0	2.0	3.0	4.0
% chloronitroso, 1 (+ 2 + 3)	18.5	24.0	39.5	70.2	87.4	96.2
% nitrimine, 4	38.8	36.6	31.8	14.2	6.2	1.7
% ketone, 5	42.7	39.2	28.7	15.6	6.4	2.1

Table V. Distribution of Products of Reaction of Nitrosyl Chloride with Pinacolone Oxime (1.0 M) and Starting Ratio [NOCl]/[Oxime] ≅ 0.5 in Chloroform at 25 °C

% oxime consumed	29	54	77	100
% chloronitroso, 1	4	10	18	21
% nitrimine, 4	13	23	32	41
% ketone, 5	12	21	27	38

Experimental Section

The NMR spectra were taken on a Varian A-60A spectrometer using Me_4Si as internal standard. A standard integration method of determining peak areas was reliable to ±4%. Each experiment with nitrosyl chloride was repeated until consistent results were obtained so that product ratios (Table II) are considered reliable to ±0.4.

Reaction of Pinacolone Oxime and Nitrosyl Chloride in Ether. To a solution of 6.0 g (0.052 mol) of pinacolone oxime in 50 ml of anhydrous ether, 4.5 ml (0.10 mol) of liquid nitrosyl chloride (purified and dried as previously described[5] was quickly added at ice-bath temperature. The solution was stirred mechanically as a white precipitate formed which soon redissolved. After 10 min, 5 g of solid sodium carbonate was added and stirred for 10 min longer. The white salts were removed by filtration and the ether was distilled at ambient pressure. Cooling the remaining green oil gave blue 2-chloro-2-ni-

troso-3,3-dimethylbutane, yield 4.5 g (60%), mp 121–122 °C (recrystallized from methanol[2,11]).

When methanol–water was used for recrystallization the white dimer of the *gem*-chloronitroso compound slowly precipitated. The dimer sublimes, 120–150 °C: ir spectrum (KBr) C–H, 2980 s; N=O, 1544 s; 742 cm^{-1} w. The ir spectra of monomer and dimer are identical except for the absence of the weak line at 742 cm^{-1} in the dimer. However, the NMR spectra of monomer and dimer are substantially different.

NMR spectra ($CDCl_3$): monomer δ 1.64 (s, 3), 1.27 (s, 9); dimer δ 2.15 (s, 3), 1.17 (s, 9).

The pale green filtrate remaining after the removal of the chloronitroso compound was diluted with ether and transferred to a silica gel column. Pinacolone nitrimine was eluted from the column as a colorless oil with a 2:1 mixture of carbon tetrachloride and benzene: yield 0.90 g (13%); bp 40 °C (2.5 mm) [lit.[12] bp 80.5–81.0 °C (12 mm)]; ir spectrum (neat) CH, 2980 br, s; C=N, 1615 m; NO_2, 1560, 1312 cm^{-1} s; NMR spectrum ($CDCl_3$) δ 2.02 (s, 3), 1.21 (s, 9).

Finally, pinacolone was removed from the column by a 1:1 mixture of benzene and chloroform, yield 0.55 g (11%). The pinacolone was identified by the strong carbonyl absorption (1640 cm^{-1}) and the NMR spectrum: ($CDCl_2$) δ 2.12 (s, 3), 1.13 (s, 9).

In this and experiments with other solvents (below), solvents could not be removed at reduced pressure because of loss of the chloronitroso compound, pinacolone, and pinacolone nitrimine in that order of decreasing volatility.

2-Chloro-2-nitro-3,3-dimethylbutane. 2-Chloro-2-nitroso-3,3-dimethylbutane (4.2 g, 0.028 mol) was heated on a steam bath with 10 ml of glacial acetic acid and 5 ml of concentrated nitric acid for 0.5 h. The reaction mixture was poured into 100 ml of cold water and extracted with 50 ml of ether. The ether solution was washed with 5% sodium carbonate solution and then with water. The ether layer was dried over anhydrous sodium sulfate. Removal of the ether by distillation and recrystallization of the product from methanol gave 2.9 g (62%) of 2-chloro-2-nitro-3,3-dimethylbutane: mp 170–172 °C (lit.[2] mp 169–170 °C); ir spectrum (KBr) C–H, 2980 br, s; NO_2, 1560, 1350 cm^{-1} s; NMR spectrum ($CDCl_3$) δ 2.17 (s, 3), 1.21 (s, 9).

Product Distribution. A. Effect of Solvent Polarity. The data for Table II and Figure 1 were obtained as follows. To a solution of 1.65 g (0.014 mol) of pinacolone oxime in 10 ml of carbon tetrachloride, 0.20 ml (0.043 mol) of liquid nitrosyl chloride was quickly added and the solution was stirred mechanically for 20 min. A sample was removed from the reaction mixture and analyzed by integration of the peaks in the NMR spectrum: chloronitroso compound (δ 1.65, 1.27); dimer (δ 2.12, 1.17); chloronitro compound (δ 2.17, 1.21); nitrimine (δ 2.03, 1.21); and ketone (δ 2.12, 1.13).

The same procedure was used with chloroform, methylene chloride, ether, and nitromethane. The dimer and the chloronitro compound appeared in less than 5% total yield in any experiment and did not interfere with the results. Repetition of each experiment more than once suggested that the limits of error in product percentage are ±2.

B. Effect of Concentration of Oxime. Pinacolone oxime (11.5 g) in 50 ml of chloroform (2 M solution) was divided into equal portions. One portion was treated with 1.8 ml (0.04 mol) of liquid nitrosyl chloride and brought to 25 °C. The other portion was diluted with an equal volume of chloroform and half the solution was treated with the same volume of liquid nitrosyl chloride at 25 °C. The second half of this solution was again diluted and so on until five concentrations (Figure 2) had been treated with the same volume of nitrosyl chloride. Each reaction mixture was analyzed as previously described to give the results shown in Figure 2 and Table III.

C. Effect of Excess Nitrosyl Chloride. At a 1 M concentration of pinacolone oxime in chloroform at 25 °C, the effect of different molar ratios of nitrosyl chloride to oxime (0.1–4.0) was analyzed in the same way. The results are given in Table IV and Figure 3.

D. Effect of Nitrosyl Chloride Addition in Small Increments. A solution of 5.8 g (0.05 mol) of pinacolone oxime in 50 ml of chloroform (1.0 M solution) was treated with 0.6 ml (0.012 mol) of liquid nitrosyl chloride. The solution was stirred for 10 min and a sample was removed for an NMR spectrum. The same increment of nitrosyl chloride was added four times more until the oxime disappeared completely from the reaction mixture (Table V). After the reaction was completed, a fifth increment of nitrosyl chloride was added and a sample was removed for an NMR spectrum after 2 and 5 h, respectively. The final product distribution was unchanged.

E. Effect of Free-Radical Inhibitors. The unlikely possibility of a free-radical mechanism being responsible for the results obtained was removed by adding free-radical inhibitors. A 2 M solution of pinacolone oxime in carbon tetrachloride (10 ml) was treated with varying amounts of iodine (0.0, 0.1, 2.5 g) in successive experiments and 1.8 ml (0.04 mol) of liquid nitrosyl chloride. The solution was stirred for 20 min and a sample withdrawn. The solution was washed with saturated sodium hydrogen sulfite solution and dried over sodium sulfate. An NMR spectrum was taken. No noticeable difference in product composition in the three experiments was observed.

The same experiments were repeated with hydroquinone in the quantities given above. The solutions were washed with water to remove unreacted hydroquinone. The same result was obtained as with the iodine inhibitor.

Registry No.—Pinacolone oxime, 2475-93-6; nitrosyl chloride, 2696-92-6; 2-chloro-2-nitroso-3,3-dimethylbutane, 677-58-7; 2-chloro-2-nitroso-3,3-dimethylbutane dimer, 58673-06-6; pinacolone nitrimine, 58673-42-0; 2-chloro-2-nitro-3,3-dimethylbutane, 57484-14-7; pinacolone, 75-97-8.

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Dewar Benzene Oxide Isomerization. A Forbidden Reaction

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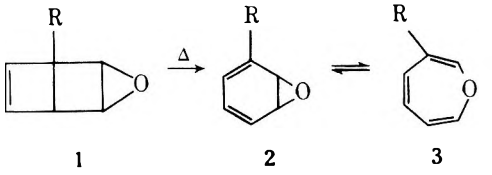
In 1967 Carty and von Tamelen reported[1] that thermolysis of Dewar benzene oxide (**1a**) afforded benzene oxide

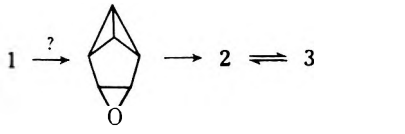


(1)

1 **2** **3**

a, R = H
b, R = D

(**2a**)-oxepin (**3a**).[2] Since a concerted least-motion mechanism for this reaction would involve a process predicted to be "forbidden" by orbital symmetry criteria,[3] we decided to determine whether such a process is, indeed, responsible for this transformation. Our idea was that a "forbidden" process should have a relatively high activation energy[3d] and, thus, the actual mechanism might be more complex[4] in order to minimize energy requirements. For example, the conversion of 1 to 2 ⇌ 3 might proceed by way of an initial isomerization to benzvalene oxide (**4**) which then



(2)

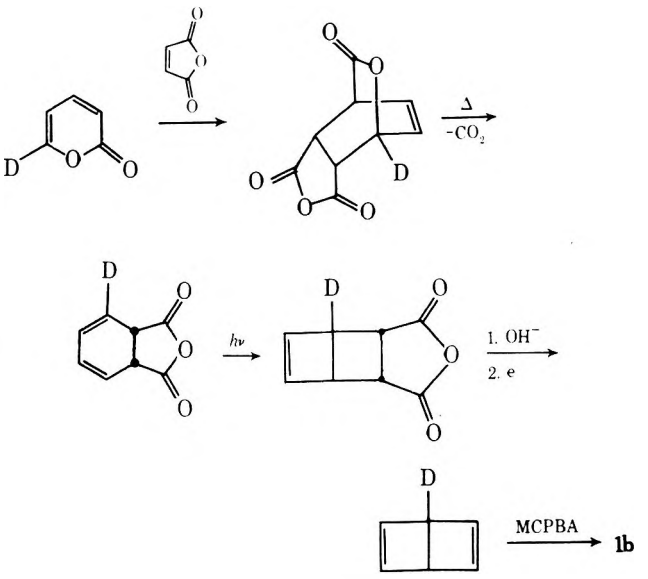
4

would undergo rearrangement to the observed products. The first step in this process is analogous to the reaction of bicyclo[2.2.0]pyran-2-one reported by Corey and Pirkle[5] and the ready thermal conversion of benzvalenes to benzene derivatives is known.[6] For the first part of this study, we selected the bridgehead labeled deuterio-Dewar benzene oxide **1b**. Such a labeling pattern would allow us to detect skeletal rearrangement occurring during the reaction.

The synthesis of **1b** was accomplished as shown in Scheme I. All of the methods used have been previously published[1,7] and the labeled materials were compared spectroscopically and, where possible, by mixture melting point with authentic unlabeled materials at each stage. The 6-*d*-pyrone was prepared by the method of Corey and Pirkle.[5] Integration of the ^{1}H NMR spectrum of **1b** indicated 102 ± 5%[8] bridgehead monodeuteration.

A sample of **1b** (0.1 M) in CCl_4 was heated at 120 ± 10 °C (sealed tube) and the reaction monitored by NMR spectroscopy. As reported for **1a**,[1] the characteristic absorptions due to the α, β, and γ protons of **2b** ⇌ **3b** (δ 5.4, 5.7, and 6.2, respectively)[2] appeared replacing in a continuous fashion those due to **1b**. **1b** exhibits a half-life under these conditions of ca. 1 h.[9] Integration of these signals afforded an α:β:γ proton ratio of 1.95 ± 0.10:1.00 ± 0.10:1.98 ± 0.10.[8]

Scheme I



This result demonstrates that **1** rearranges to **2** ⇌ **3** in the straightforward manner.

The second part of this study involved a determination of the activation energy for the isomerization. Sealed samples of **1a** (0.05 M) in tetrachloroethene were heated at 97.8 and 109.5 (±0.2) °C and the progress of the reaction monitored by NMR spectroscopy. Each reaction was followed for at least 2 half-lives and a plot of log [**1a**] vs. time afforded a straight line in each case. The rate constant for the rearrangement was 3.4×10^{-5} s^{-1} at 97.8 °C and 1.2×10^{-4} s^{-1} at 109.5 °C.

The derived free energy of activation at 97.8 °C is 29 ± 3 kcal/mol.[10] The limited nature of these data does not allow a reliable calculation of the activation enthalpy and entropy.

These results suggest that the thermal isomerization of **1a** resembles that of Dewar benzene itself ($\Delta G^{\ddagger}$ = 25 kcal/mol[11]). They are consistent with both fully concerted[12] (symmetrical) and biradical mechanisms. Dewar has reported calculations[3d] which indicate that the favored pathway for a thermal disrotatory cyclobutene opening involves an unsymmetrical transition state. Further mechanistic discussion should await a determination of whether **2** or **3** is the initial reaction product.

Experimental Section

General. Proton magnetic resonance spectra were determined on a Varian Associates T-60 instrument. The labeled and unlabeled Dewar benzene oxides were prepared by the method of van Tamelen and Carty.[1] The labeled dihydrophthalic anhydride was prepared by the cycloaddition of maleic anhydride and 6-*d*-pyrone[5] followed by decarboxylation in boiling xylene by the method of Goldstein and Thayer.[7b]

Pyrolysis of 3-Oxatricyclo[3.2.0.0^{2,4}]hept-6-ene-*1-d* (1b). A sample of **1b** (5.0 mg, 0.053 mmol) in 0.5 ml of carbon tetrachloride was sealed in an NMR tube.[13] This tube was then inserted in an oil bath kept at 120 ± 10 °C on a hot plate. The reaction progress was monitored by periodically removing the NMR tube from the oil bath and determining the spectrum. Careful integration of the starting material and product[2] proton absorptions showed that 52 ± 3% of **1b** had been converted to **2b** ⇌ **3b** in 60.0 min. The heat-

ing was continued for a total of 240 min before the final NMR analyses were done.

Pyrolysis of 3-Oxatricyclo[3.2.0.0^{2,4}]hept-6-ene (1a). Sealed tubes[13] of **1a** in tetrachloroethene were inserted in the condensing vapors of toluene (109.5 °C) and *p*-dioxane (97.8 °C) and the reaction progress monitored by NMR spectroscopy.

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Registry No.—**1a**, 16622-65-4.

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2-Acyloxymethylbenzoic Acids. Novel Amine Protective Functions Providing Amides with the Lability of Esters

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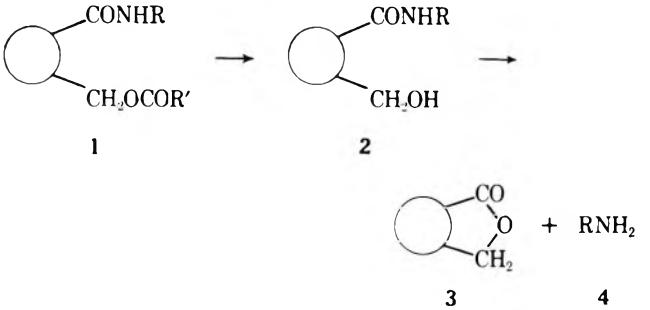
To confer more desirable pharmacokinetic properties on certain antitumor agents a novel drug latentiation scheme was earlier proposed.[2] To release agent from the latentiated derivatives a trigger mechanism utilizing a hydroxy acid component was suggested; elimination of the hydroxy acid unit as the corresponding lactone would release the core antitumor agent. In the example provided (Scheme I) the carbonyl group of the hydroxy acid component is linked to drug –NH– in an amide bond. Such hydroxy amides (**2**) are relatively unstable, the products of intramolecular hydroxyl group attack on amide carbonyl being the lactone **3** and amine **4**. Masking of hydroxyl function in **2** by acylation provides stable derivatives **1** which can be readily manipulated and purified. It was envisaged that in vivo serum esterase action on such acyl derivatives (**1**), by providing the unstable hydroxylic compound **2**, could trigger the release of the core species **4**.

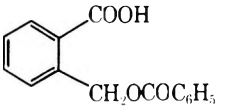
Scheme I



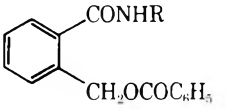
1 2 3 4

Similarly in vitro, any chemical treatment resulting in ester cleavage or exchange in the acyloxy amides (**1**) could result in liberation of the amine component **4**. Such amides might then also be useful for the protection of amino groups during synthesis with the ultimate ease of demasking approaching the ease of cleavage of an ester.

For the preparation of acyloxy amides of type **1** the most readily available precursors are the lactones but no directly useful example of a reaction for conveniently modifying a lactone could be found. Possibly the simplest method of obtaining useful intermediates from lactone precursors, Schotten–Baumann acylation of alkaline hydrolysates of a lactone, appears not to have been successfully applied. Employing phthalide as a model compound it was found that addition of benzoyl chloride to alkaline solutions of this lactone provided 2-benzoyloxymethylbenzoic acid (**5**) in 62% yield. Attempted acid chloride preparation from this acid with thionyl chloride alone returned phthalide and benzoyl chloride. However, by inclusion of 1 mol of pyridine in such reactions crystalline 2-benzoyloxymethylbenzoyl chloride could be isolated in 89% yield. From this acid chloride amide derivatives and the 4-nitrophenyl ester could be readily prepared. The latter 4-nitrophenyl ester also resulted from the action of tri(4-nitrophenyl) phosphite on the acid **5** in pyridine solution. The 4-nitrophenyl ester with suitable amines also furnished amide derivatives and phosphorazo[3,4] coupling of amines and **5** provided a further route to the amides.



5



6a, R = CH_2CONH_2
b, R = 4-$CH_3C_6H_4$

An aliphatic (**6a**) and an aromatic amide (**6b**) of 2-benzoyloxymethylbenzoic acid were prepared and subjected to usually employed reagents and conditions for protective group removal in peptide synthesis;[5] details are tabulated in Table I. The first reagent listed (NaOMe–MeOH) is not normally applied in peptide chemistry but is commonly employed to catalyze ester exchange. It can be noted that those reagents which are normally considered to promote ester hydrolysis or exchange are those which produced amide cleavage in **6a** and **6b** (Table I).

For drug latentiation purposes 2-acyloxymethyl functions other than that containing the lipophilic benzoyl residue were desired. Use of acetic anhydride in the initial Schotten–Baumann conditions provided mixtures and TLC of these showed that the desired 2-acetoxymethylbenzoic acid was being produced but the marked lability of this, providing acetic acid and phthalide, prevented com-

Table I[a]

Reagents and conditions	6a	6b
NaOMe–MeOH, 20 °C	Cleaved[b]	Cleaved[b]
1 N HCl–MeOH, 20 °C	Cleaved[c]	Cleaved[d]
80% HOAc, 15 min, 100 °C	Unchanged	Unchanged
CF_3COOH, 1 h, 20 °C	Unchanged	Unchanged
2 N HBr–HOAc, 30 min, 20 °C	Unchanged	Unchanged
1 N NaOH–80% MeOH, 1 h, 20 °C	Cleaved	Cleaved
45 psi H_2–10% Pd/C, 20 °C	Reduced[e]	Reduced[f]

[a] Reactions were monitored by TLC and the nature of the products confirmed by isolation and direct comparison with authentic samples. Unless otherwise noted the products of cleavage were phthalide and glycinamide from **6a** and phthalide and *p*-toluidine from **6b**. [b] Extremely rapid; reaction complete on mixing. [c] Slow reaction, 48 h necessary for complete reaction of ninhydrin reactive product then glycine methyl ester. [d] Slow, 48 h necessary for completion. [e] Product 2-(2-methylbenzamido)acetamide. [f] Product 2-methyl-*N*-(4-methylphenyl)benzamide.

plete purification. In contrast to most other acylating agents tried, acyl cyanides[6,7] were found to selectively acylate hydroxyl functions without affecting carboxylate anions. For example, the potassium salt of 2-hydroxymethylbenzoic acid in DMF solution with benzoyl cyanide provided the potassium salt of 2-benzoyloxymethylbenzoic acid. Final addition of tri(4-nitrophenyl) phosphite to such reaction mixtures provided 2-benzoyloxymethylbenzoic acid 4-nitrophenyl ester directly. By using equivalent conditions isolation of the unstable 2-acetoxymethylbenzoic acid could then be avoided; reaction of potassium 2-hydroxymethylbenzoate and acetyl cyanide in DMF with following addition of tri(4-nitrophenyl) phosphite provided the stable 2-acetoxymethylbenzoic acid 4-nitrophenyl ester.

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus with the makers supplied stem corrected thermometer; melting points are as read. Analyses were performed by Dr. A. D. Campbell, Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Ir spectra (KBr) were recorded on a Beckman 237 Infracord. Uv spectra were recorded on a Shimadzu UV-200.

Chromatography used Merck SiO_2 F_{254} Al TLC sheets.

2-Benzoyloxymethylbenzoic Acid (5). Method A. Phthalide (15 mmol) was dissolved by heating in aqueous NaOH (12.5 ml of 20%) and the solution cooled to 5 °C. Crushed ice (100 g) was added and vigorous sweep stirring instituted. Benzoyl chloride (2.7 ml) was added in one portion and stirring continued until the odor of benzoyl chloride disappeared. Ice-cold HCl (25 ml, 2 N) precipitated crude acid, which, after washing well with hot water (60 °C) and drying, was crystallized from C_6H_6–light petroleum. Further crystallization from *n*-BuOH provided pure material as massive prisms, mp 128–129 °C (2.37 g, 62%), ir 1686, 1715 cm^{-1}.

Method B. Potassium 2-hydroxymethylbenzoate was prepared by solution of phthalide (6 mmol) and KOH (6 mmol) in 85% MeOH–H_2O, boiling for 30 min, then evaporating to dryness and drying at 110 °C in vacuo. The crystalline salt was dissolved by warming in dry DMF (12 ml) and the solution cooled to below 0 °C. Benzoyl cyanide (12 mmol) was then stirred in. After 30 min of stirring at this temperature Et_3N (0.05 ml) was added and stirring continued for 30 min more. Following addition of MeOH (20 mmol) and stirring for 10 min as much solvent as possible was removed in vacuo at steam bath temperature. The residue was dissolved in cold H_2O (15 ml) and neutrals (methyl benzoate and phthalide) removed by Et_2O extraction. After vacuum stripping of Et_2O from the aqueous phase acidification at 0 °C precipitated crude acid. Crystallization as above gave pure acid (87% yield) of the same melting point, mixture melting point, and TLC behavior.

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.3; H, 4.7. Found: C, 70.5; H, 4.8.

2-Benzoyloxymethylbenzoyl Chloride. To a suspension of the above acid (4.7 mmol) in C_6H_6 (2 ml) was added Py (4.7 mmol) followed by freshly redistilled $SOCl_2$ (5 ml). After 10 min of boiling the solution was concentrated in vacuo and the remaining solid extracted with dry, boiling C_6H_6 (3 × 25 ml). Evaporation provided the acyl chloride as a thick oil which crystallized on trituration with light petroleum. One crystallization from light petroleum provided product as large prisms, mp 47–49 °C (1.2 g, 89%). Further crystallization raised the melting point to 51–52 °C.

Anal. Calcd for $C_{15}H_{11}O_3Cl$: C, 65.6; H, 4.0; Cl, 12.9. Found: C, 66.0; H, 4.0; Cl, 12.9.

2-Benzoyloxymethylbenzoic acid 4-nitrophenyl ester was isolated from H_2O-diluted reaction mixtures by extraction into EtOAc, washing of the organic layer with 10% Na_2CO_3, 2 N HCl, and 20% NaCl, drying (Na_2SO_4), and evaporation. Crystallization was from MeOH monitoring homogeneity by TLC.

Method C. Reaction of 2-benzoyloxymethylbenzoyl chloride (10 mmol) with a solution of 4-nitrophenol (11 mmol) in Py (10 ml) on the steam bath for 30 min provided product in 89% yield.

Method D. A solution of tri(4-nitrophenyl) phosphite was prepared by dropwise addition of PCl_3 (3 mmol) to a well-cooled solution of 4-nitrophenol (10 mmol) in excess Py. Addition of acid **5** (6 mmol) and 30 min of heating on the water bath gave, after workup, a 72% yield of pure ester.

Method E. A DMF solution of the potassium salt of 2-benzoyloxymethylbenzoic acid was prepared exactly as in method B but MeOH was not then added. A solution of tri(4-nitrophenyl) phosphite from 4-nitrophenol (11 mmol) and PCl_3 (3 mmol) in Py was then added and after 30 min of heating on the steam bath as much solvent as possible was removed in vacuo.

Pure product separated from MeOH as colorless, glistening plates, mp 78.5–79 °C.

Anal. Calcd for $C_{21}H_{15}NO_6$: C, 66.7; H, 4.0; N, 3.7. Found: C, 66.9; H, 4.0; N, 3.4.

2-[2-(Benzoyloxymethyl)benzamido]acetamide (6a). 2-Benzoyloxymethylbenzoic acid (2 mmol) and glycinamide hydrochloride (2 mmol) were suspended in Py (25 ml) and the whole stirred while cooling to −5 °C. Et_3N (6.5 mmol) was added and then PCl_3 (1.33 mmol) in dropwise fashion maintaining the temperature below 0 °C. After stirring at 0° for 24 h excess Py was removed in vacuo, H_2O added, and product removed in EtOAc. The extracts were washed with 2 N HCl, 10% $KHCO_3$, and 20% NaCl, dried (Na_2SO_4), and evaporated. Shaking with light petroleum initiated crystallization. Recrystallization was by solution in excess boiling EtOAc, clarification, then distillation of solvent until crystallization commenced. Pure product (78% yield) was obtained as colorless needles, mp 206–207 °C.

Alternatively, the corresponding 4-nitrophenyl ester (3 mmol) and glycinamide hydrochloride (3 mmol) were suspended in DMF (7.5 ml) at room temperature and Et_3N (3 mmol) was added to the stirred suspension. After 48 h at room temperature isolation, as above, provided product (72% yield) having the same melting point, mixture melting point, and TLC behavior.

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.4; H, 5.2; N, 9.0. Found: C, 65.4; H, 5.0; N, 8.9.

2-(Benzoyloxymethyl)-*N*-(4-methylphenyl)benzamide (6b). Reaction between 2-benzoyloxymethylbenzoyl chloride and *p*-toluidine in Py in the usual fashion provided this product (91% yield). Alternatively, addition of PCl_3 (2 mmol) to a solution of acid (3 mmol) and amine component (3 mmol) in excess Py and isolation, as in other examples, provided an 87% yield of product. Pure product separated from EtOH–H_2O as colorless plates, mp 102–103 °C.

Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.6; H, 5.6; N, 4.1 Found: C, 76.6; H, 5.7; N, 4.3.

2-Acetoxymethylbenzoic Acid 4-Nitrophenyl Ester. Acetyl cyanide was prepared from acetyl bromide and cuprous cyanide[8] and had bp 93–93.5 °C (760 mm) [lit.[8] 93 °C (760 mm)]. A solution of potassium 2-hydroxymethylbenzoate (12 mmol) in dry DMF (30 ml) was stirred at 0 °C and acetyl cyanide (24 mmol) added. After 30 min of stirring Et_3N (0.02 ml) was added and stirring continued for another 1 h when a solution of 4-nitrophenol (18 mmol) and PCl_3 (6 mmol) in Py (15 ml) was added. The mixture was heated at 100 °C for 30 min and then solvents removed in vacuo. Product was removed in EtOAc in the usual way after addition of water. The gummy residue obtained on removal of EtAc crystallized on rubbing with light petroleum. Two crystallizations from EtOH provided TLC-homogenous material as colorless plates of mp 112–113 °C (52% yield).

Anal. Calcd for $C_{16}H_{13}NO_6$: C, 60.9; H, 4.2; N, 4.5. Found: C, 61.1; H, 4.3; N, 4.8.

2-(2-Methylbenzamido)acetamide. Hydrogenation (45 psi H_2)

in EtOH solution of **6a** at 20 °C over 10% Pd/C catalyst provided a product crystallizing from absolute EtOH as colorless needles, mp 206–207 °C.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.3; N, 14.6. Found: C, 62.8; H, 6.4; N, 14.8.

Phosphorazo coupling[6,7] of 2-methylbenzoic acid and glycinamide, as in earlier examples, provided a product which was identical by melting point, mixture melting point, and TLC criteria with that obtained from the hydrogenation.

In similar fashion hydrogenation of **6b** provided 2-methyl-*N*-(4-methylphenyl)benzamide, mp 143.5–144 °C, identical in melting point, mixture melting point, and TLC behavior with a synthesized sample.

Registry No.—**5**, 58249-83-5; **6a**, 58249-84-6; **6b**, 58249-85-7; phthalide, 87-41-2; benzoyl chloride, 98-88-4; potassium 2-hydroxymethylbenzoate, 58249-86-8; benzoyl cyanide, 613-90-1; 2-benzoyloxymethylbenzoyl chloride, 58249-87-9; 2-benzoyloxymethylbenzoic acid 4-nitrophenyl ester, 58249-88-0; 4-nitrophenol, 100-02-7; tri(4-nitrophenyl) phosphite, 23485-35-0; glycinamide, 598-41-4; *p*-toluidine, 106-49-0; acetyl cyanide, 631-57-2; 2-(2-methylbenzamide)acetamide, 6754-94-5; 2-methyl-*N*-(4-methylphenyl)-benzamide, 58249-89-1.

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(1) This work was supported by the Auckland Division of the New Zealand Cancer Society Inc., and in part by the Medical Research Council of New Zealand.
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Synthesis of 2-Benzyl-4-phenyl-2,4-dihydropyrrolo[3,4-*b*]indole

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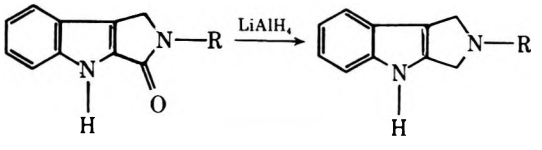
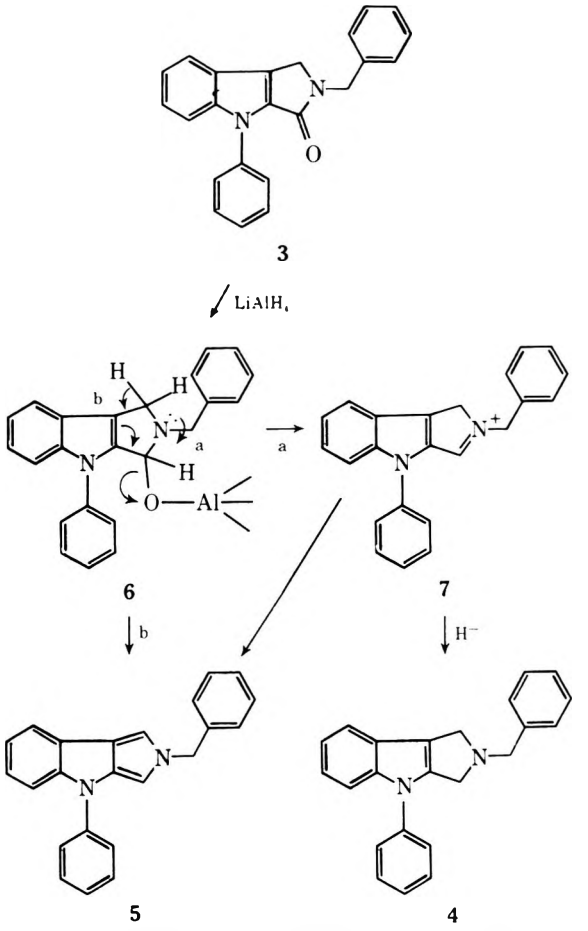
The preparation of a limited number of 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles has been reported in the literature, but no compounds of the corresponding 2,4-dihydropyrrolo[3,4-*b*]indole series have been described. We report here the preparation of the first example of this series via lithium aluminum hydride reduction of the corresponding 2-benzyl-1,4-dihydropyrrolo[3,4-*b*]indol-3(2*H*)-one.

The preparation of 2-substituted 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles (**2**) through $LiAlH_4$ reduction of the corresponding pyrrolo[3,4-*b*]indol-3(2*H*)-ones (**1**) at elevated temperatures has been reported by Southwick and Owellen.[1] In conjunction with investigations of the chemistry of 2-substituted pyrrolo[3,4-*b*]indoles bearing a phenyl substituent in the 4 position it was decided to adapt this procedure to our series. Thus, 2-benzyl-4-phenylpyrrolo[3,4-*b*]indol-3(2*H*)-one (**3**), prepared in excellent yield from 1-benzyl-2,3-pyrrolidinedione[2] and diphenylhydrazine, when reduced by the procedure of Southwick and Owellen afforded two major products which were readily separated by silica gel chromatography.



1 **2**



3 **6** **7** **5** **4**

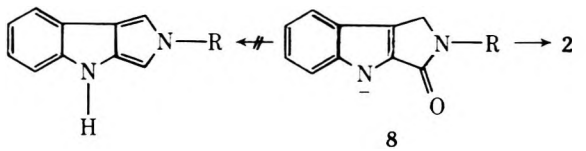
The more polar of these was identified as the expected 2-benzyl-4-phenyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (**4**) through spectral and analytical data. Spectral and analytical data obtained on the less polar, relatively stable (>4 weeks at 0 °C) product as the free base or picrate salt confirmed its structure as 2-benzyl-4-phenyl-2,4-dihydropyrrolo[3,4-*b*]indole (**5**). The relatively simple mass spectrum of **5** consisted of the parent ion (*m/e* 322, base peak) and an ion at *m/e* 231 representing loss of the tropylium ion, indicating a highly stable nucleus. In the NMR spectrum of **5**, only the benzyl methylene protons at δ 4.91 lie outside the aromatic region, although both the C(1) and C(3) methine protons can be observed. Proton decoupling experiments demonstrate that these protons are coupled to each other with a coupling constant of 1.8 Hz, consistent with values established for 2,5-proton coupling in pyrrole and its derivatives.

The formation of a dihydropyrrolo[3,4-*b*]indole under these conditions represents a novel and unprecedented action of $LiAlH_4$ which may be rationalized through the following mechanistic considerations. Formation of **7**, the immonium precursor of **4** (path a), by elimination of an oxyaluminum species from the initially formed **6** generates considerable ring strain in the 6-5-5 ring nucleus and is probably not favored energetically. The relative stability of **6** thus allows a second mechanism (path b) to become operative, that is, the abstraction of a relatively acidic (due to polarization of the C(3)–N bond) C(1) proton generating **5** via the 1,4 elimination illustrated. Alternatively, proton abstraction from C(1) in **7** could yield **5**. This pathway is deemed less likely, owing to the known rapid addition of hydride ion to such immonium species.

Further evidence in support of either of these mechanisms was obtained through the reduction of **3** in the presence of the soluble tertiary amine base *N*-ethylpiperidine (bp 130 °C). The yield of **5** under these conditions was increased from 27% to 42% (the yield of **4** remaining the same) reflecting a more

efficient abstraction of the C(1) proton by soluble base. It is of interest to note that energetic requirements for operation of either mechanism appear to be high, since our attempted reductions at lower temperatures were unsuccessful. The reduction of α,β-unsaturated γ-lactones to the corresponding furans with dialkylaluminum hydrides has been reported[3] to proceed at low (−20 to −25 °C) temperatures in good yield. This difference most likely reflects the energy differences between formation of the pseudoaromatic furan ring and disruption of the indole nucleus to form **5**.

It is of interest to note that Southwick did not report formation of dihydropyrrolo[3,4-*b*]indoles **9** from N(4) unsubstituted pyrrolo[3,4-*b*]indolones **1**, although yields of the tetrahydro species and conditions of reduction were comparable. Owing to the relative acidity of indole nitrogen protons, it is quite likely that generation of the N(4) anion (i.e., **8**) in Southwick's series would prevent abstraction of a proton from C(1) and hence the elimination sequence envisioned in path b above. Also of interest is the stability of these compounds by comparison with that of isoindoles.[4] Clearly the subject compounds resemble disubstituted pyrroles rather than the isoindole type of molecule. This stability and the extended chromophore apparent from our uv data imply (but do not confirm) electronic interaction between the rings of this interesting molecule.



9 **8**

Experimental Section[5]

2-Benzyl-4-phenylpyrrolo[3,4-*b*]indol-3(2*H*)-one (3). A solution of 11.90 g (63.0 mmol) of 1-benzyl-2,3-pyrrolidinedione in 200 ml of glacial acetic acid was added to a suspension of diphenylhydrazine hydrochloride (13.88 g, 63.0 mmol) in 200 ml of glacial acetic acid and the resulting suspension was heated briefly on a steam bath to effect hydrazone formation. Then 100 ml of concentrated hydrochloric acid was added to the warm solution and heated for a further 20 min. The reaction mixture was diluted slowly with water giving 17.8 g (84%) of crystalline **3**. Recrystallization from ethyl acetate gave colorless crystals, mp 145.5–146.5 °C: ir (KBr) 3.35, 3.52, 5.97, 6.91, 7.25, 8.15, 13.17, 13.40 μ; NMR ($CDCl_3$) δ 4.30 (2 H, s), 4.75 (2 H, s), 7.12–7.76 (9 H, m), 7.30 (5 H, s); uv (MeOH) λ_{max} 246 nm (log ϵ 4.265), 299 nm (4.141); mass spectrum *m/e* 338 (parent ion). Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.66; H, 5.33; N, 8.28. Found: C, 81.35; H, 5.51; N, 8.24.

2-Benzyl-4-phenyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (4) and 2-Benzyl-4-phenyl-2,4-dihydropyrrolo[3,4-*b*]indole (5). To a solution of 13.0 g (38.5 mmol) of **3** dissolved in 350 ml of dry toluene (4A molecular sieves) at reflux was added 2.92 g (76.9 mmol) of $LiAlH_4$. The resulting suspension was heated at reflux for 16 h and then cooled to room temperature. After the slow addition of 150 ml of ethyl acetate, 150 ml of water was added and the resulting suspension was filtered. The separated aluminum salts were washed thoroughly with ethyl acetate and the washings combined with the filtrate. The aqueous phase was extracted thoroughly with ethyl acetate, the combined organic extracts were then dried ($MgSO_4$), and the solvent was evaporated to give 17 g of an orange oil. This material was chromatographed on 340 g of Brinkmann silica gel. The benzene eluent consisted of 3.39 g of an oil (R_f 0.75, benzene) and the 1:1 benzene–ethyl acetate fraction was 5.16 g of an oil (R_f 0.11, benzene). Neither product could be induced to crystallize; however, the less polar product, identified below as **5**, yielded a crystalline picrate salt from ethanol whereas the more polar product **4** formed a crystalline hydrochloride salt from ether with dry HCl gas.

2-Benzyl-4-phenyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole Hydrochloride (4): mp 198.0–199.5 °C; mass spectrum *m/e* 324 (parent ion), 323 (M − 1, 100%), 232, 218, 204, 91; NMR ($CDCl_3$) δ 4.47 (4 H, d),[6] 4.69 (2 H, d),[6] 6.94–7.50 (12 H, m), 7.50–7.74 (2 H, m); uv (MeOH) λ_{max} 254 nm (log ϵ 4.159), 287 (3.963).

Anal. Calcd for $C_{23}H_{20}N_2$·HCl: C, 67.54; H, 5.87; N, 7.76. Found: C, 67.23; H, 5.95; N, 7.71.

2-Benzyl-4-phenyl-2,4-dihydropyrrolo[3,4-*b*]indole Picrate (5): mp 134–135 °C; mass spectrum *m/e* 323 (parent ion, 100%); NMR (free base, $CDCl_3$) δ 4.91 (2 H, s), 6.37 (1 H, d, J = 1.5 Hz), 6.73 (1 H, d, J = 1.5 Hz), 6.80–7.67 (14 H, m); uv (MeOH) λ_{max} 250 nm (log ϵ 4.065), 270 (3.807), 282 (3.817), 303 (3.678).

Anal. Calcd for $C_{23}H_{18}N_2$·$C_6H_3N_3O_7$: C, 63.16, H, 3.84; N, 12.70. Found: C, 63.19; H, 3.93; N, 12.85.

Reduction of 3 with $LiAlH_4$ in the Presence of *N*-Ethylpiperidine. A solution of 0.50 g (4.4 mmol) of distilled *N*-ethylpiperidine and 0.50 g (1.48 mmol) of compound **3** in 15 ml of dry toluene was heated to reflux at which time 0.11 g (2.89 mmol) of $LiAlH_4$ was added. Reflux was continued for 16 h. Then the reaction mixture was cooled, worked up, and subjected to column chromatography as outlined above. The benzene eluent yielded 200 mg (42%) of compound **5** and the 1:1 benzene–ethyl acetate fractions contained 218 mg (45%) of compound **4** identical in all respects with the compounds described above.

Acknowledgment. We are grateful to Dr. E. B. Whipple and associates for the proton decoupling experiments and to Mr. R. L. Taylor and Mr. F. C. Kohansky for valuable technical assistance.

Registry No.—**3**, 58485-96-4; **4** HCl, 58485-97-5; **5** picrate, 58485-99-7; 1-benzyl-2,3-pyrrolidinedione, 58485-00-3; diphenylhydrazine HCl, 29666-92-0; *N*-ethylpiperidine, 766-09-6; $LiAlH_4$, 16853-85-3.

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(4) For example, see J. D. White and M. E. Mannin, *Adv. Heterocycl. Chem.*, **10**, 113 (1969).
(5) Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as internal standard. Proton decoupling experiments were conducted on a Varian XL-100 spectrometer. Ir spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. Uv spectra were recorded on a Cary Model 14 spectrophotometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. All evaporations were conducted in vacuo using either a water aspirator or a vacuum pump.
(6) It is apparent that, in the hydrochloride salt, the α and β C(1) and C(3) methylene protons are nonequivalent owing to the quaternary nature of N(2). In NMR spectra of the free base of **4**, this region collapses to a 6 H singlet at δ 4.10.

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s-Triazines. 1. Reaction of Cyanuric Chloride with Unsaturated Nitrogen Compounds

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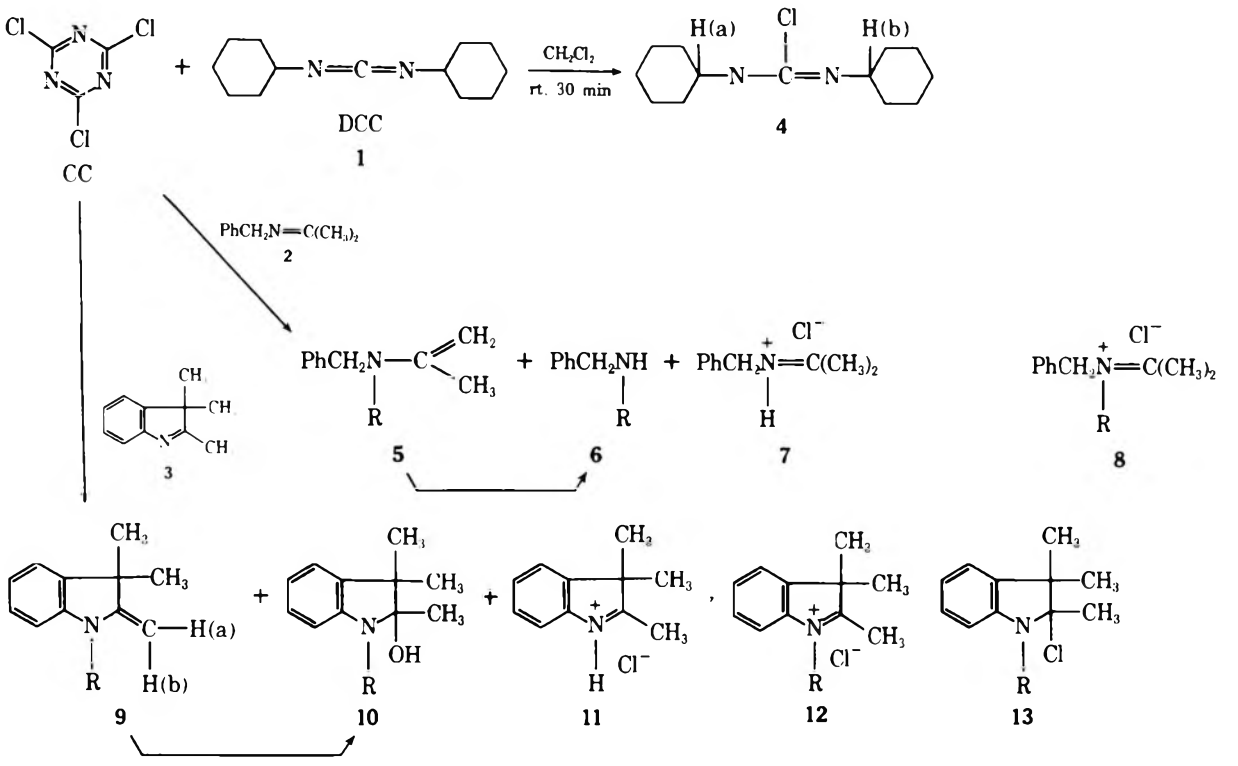
Received December 22, 1975

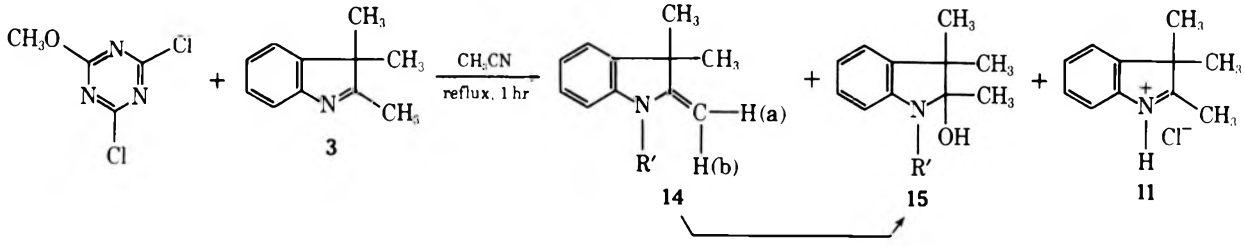
Since 1940 applications of *s*-triazine derivatives, especially melamine and its derivatives, have been extended into nearly every industrial field.[1] In addition, many melamine derivatives have been found to exhibit[1,2,3] antineoplastic, antibiotic, antibacterial, and/or insecticidal activity. We believe, therefore, that other hitherto unknown *s*-triazines, especially melamine derivatives, will probably have potential antineoplastic and antibiotic action.

Although several synthetic methods for the preparation of *s*-triazine derivatives from cyanuric halides have been developed,[1] few studies have been reported of the reaction of cyanuric halides with unsaturated nitrogen compounds other than pyridine.[4] In the course of work on potential anticarcinogens we have found that cyanuric chloride (CC) reacts at room temperature with dicyclohexylcarbodiimide (DCC, **1**),

Scheme I



Scheme II



N-isopropylidenebenzylamine (**2**), and 2,3,3-trimethylindolenine (**3**).

DCC (**1**, 1 equiv) reacts with CC to form 2,4-dichloro-6-[*N'*-cyclohexyl-*N'*-(*N'*-cyclohexylchloroimino)]-*s*-triazine (**4**) in 95% yield (Scheme I). Also, we obtained a small amount of a pale yellow solid which was amorphous in several solvent systems and showed several bands on TLC.

2,4-Dichloro-6-(*N'*-benzyl-*N'*-isopropenyl)-*s*-triazine (**5**) and 2,4-dichloro-6-benzylamino-*s*-triazine (**6**)[5] were obtained in 11 and 3 yield, respectively, from the base **2** (1 equiv). Also, *N*-isopropylidenebenzylamine hydrochloride (**7**) was obtained in 4 yield. When 2 equiv of the base was used, **5**, **6**, and **7** were obtained in 63, 30, and 94% yield, respectively, calculated on the basis of CC. No compound of structure **8** was isolated from either of the reactions. Pure **5** was converted to **6** at room temperature within 1 day, although **5** was stable enough to be separated by preparative TLC.

From the indolenine **3** (1 equiv), 2,4-dichloro-6-(2'-methylene-3',3'-dimethylindoline)-*s*-triazine (**9**) and 2,4-dichloro-6-(2'-hydroxy-2',3',3'-trimethylindoline)-*s*-triazine (**10**) were obtained in 3.4 and 41% yield, respectively. Also, the hydrochloride **11** was obtained in 50% yield. Neither **12** nor **13**[6] was isolated.

It is of interest that the ratio of **9** and **10**, which was 3:1[7] before isolation by TLC, changed to 1:12 after the procedure, although TLC of pure **9** showed no detectable conversion to **10**, which was checked by NMR spectrum. Compounds **9** and **11** were obtained quantitatively by using 2 equiv of the indolenine **3**, one of which was used as a scavenger of hydrogen chloride produced in the reaction.

It was also found that 2,4-dichloro-6-methoxy-*s*-triazine reacted with the active azomethine (–C=N–) group under more vigorous conditions (in refluxing dry CH_3CN, for 1 h). From **3** (2 equiv), **11**, 2-chloro-4-methoxy-6-(2'-methylene-3',3'-dimethylindoline)-*s*-triazine (**14**), and 2-chloro-4-methoxy-6-(2'-hydroxy-2',3',3'-trimethylindoline)-*s*-triazine (**15**) were obtained in 96, 24, and 48% yield, respectively, calculated on the basis of the *s*-triazine (Scheme II). The indolenine **3** (3%) was recovered. Again, the addition of water to **14** took place. The ratio of **14** and **15** (2:1)[8] changed to 2:5 after isolation and purification. It is not clear at this time what causes these observed ratio changes of **9**/**10** and **14**/**15** during the process.

Experimental Section

All NMR spectra (60 MHz) were determined in $CDCl_3/Me_4Si$. All ir spectra were determined in a KBr mix. Silica gel, GF_{254} (E. Merck), was used for preparative TLC.

General Procedure for the Reactions. To CC (922 mg, 5 mmol) suspended in dry CH_2Cl_2 (5 ml), a solution of the substrate (5 or 10 mmol) in CH_2Cl_2 (2 or 4 ml) was added dropwise at room temperature

over a period of several minutes with vigorous stirring. After 30 min the solvent was removed by an aspirator at room temperature and the residue was purified by usual techniques.

Reaction of CC with DCC (1). The residue obtained from CC and DCC (1.03 g, 5 mmol) was dissolved in *n*-hexane and the amorphous pale yellow solid was filtered off. The solution was condensed and kept in a refrigerator to give colorless prisms of **4** (1.85 g, 95%): mp 101 °C; ir 1690 cm^{-1} (C=N); NMR δ 4.41 [1, m, methyne H(a)], 3.70 [1, m, methyne H(b)], 2.30–1.00 (20, m, dicyclohexyl H); *m/e* 339 ($M\cdot^+$, 0.0001), 354 ($M\cdot^+ - \cdot Cl$, 0.01), 308 ($M\cdot^+$ − cyclohexenyl radical, 0.11).

Anal. Calcd for $C_{16}H_{22}Cl_3N_5$: C, 49.16; H, 5.63; N, 17.97. Found: C, 48.99; H, 5.62; N, 17.91.

Reaction of CC with *N*-Isopropylidenebenzylamine (2). The residue obtained from CC and the imine (735 mg, 5 mmol) was extracted with anhydrous Et_2O under a nitrogen atmosphere. The insoluble solid was dissolved in dry CH_2Cl_2 and anhydrous Et_2O was added to the solution slowly to give colorless needles of **7** (440 mg, 48%): mp 114–118 °C;[9] ir 2630 and 1690 cm^{-1} (C=N⁺<); NMR δ 7.60–7.10 (5, m, aromatic H), 4.82 (2, s, $-CH_2Ph$), 2.70 and 2.41 [6, s, $(CH_3)_2C=$].

Anal. Calcd for $C_{10}H_{13}N\cdot HCl$:[10] C, 65.39; H, 7.62; N, 7.62. Found: C, 64.13; H, 7.44; N, 7.73.

The ether filtrate was chromatographed by preparative TLC developed with benzene to give two main bands, which were extracted with CH_2Cl_2. The solution from the upper band was distilled to give **5** as a colorless liquid (162 mg, 11%): bp 125–126 °C (0.15 mm);[11] ir (NaCl) 1665 cm^{-1} (C=C); NMR δ 7.27 (5, s, aromatic H), 5.10 and 4.85 (2, d, J = 1.8 Hz, vinylic H), 4.95 (2, s, $-CH_2Ph$), 1.84 (3, s, $-CH_3$); *m/e* 203 ($M\cdot^+ - \cdot C_7H_7$, 64.2).

Anal. Calcd for $C_{13}H_{12}Cl_2N_4$: C, 52.88; H, 4.06; N, 18.98. Found: C, 52.63; H, 4.09; N, 19.32.

The product from the other band was crystallized from *n*-hexane to give colorless prisms of **6** (484 mg, 38%), identical with an authentic sample.[5]

From 10 mmol of the imine, the compounds **5** (929 mg, 63%), **6** (383 mg, 30%), and **7** (865 mg, 93%) were obtained by the same procedure as above.

Reaction of CC with 2,3,3-Trimethylindolenine (3). The residue obtained from CC and the indolenine (795 mg, 5 mmol) was extracted with anhydrous Et_2O followed by preparative TLC developed with a mixture of *n*-hexane and benzene (3:1 v/v) to give two main bands, which were extracted with CH_2Cl_2 and crystallized from *n*-hexane, respectively. The upper band was assigned as **9** (52 mg, 3.4%): mp 122–123 °C; ir 1650 cm^{-1} (C=C); NMR δ 8.41 (1, m, C_7· H), 7.43–7.10 (3, m, aromatic H), 6.37 [1, d, J = 1.0 Hz, olefinic H(b)], 5.80 [1, d, J = 1.0 Hz, olefinic H(a)], 1.43 [6, 3′,3′-$(CH_3)_2$]; *m/e* 306 ($M\cdot^+$, 47.6), 291 ($M\cdot^+ - \cdot CH_3$, 100).

Anal. Calcd for $C_{14}H_{12}Cl_2N_4$: C, 54.72; H, 3.90; N, 18.24. Found: C, 54.80; H, 4.11; N, 18.24.

The other band was assigned as **10** (674 mg, 41%): mp 128–129.5 °C; ir 3485 cm^{-1} (–OH); NMR δ 8.13 (1, m, C_7· H), 7.15–7.05 (3, m, aromatic H), 5.75 (1, s, –OH), 1.75 (3, s, 2′-CH_3), 1.39 and 1.22 [6, s, 3′,3′-$(CH_3)_2$]; *m/e* 324 ($M\cdot^+$, 27.5), 306 ($M\cdot^+ - H_2O$, 17.7), 291 ($M\cdot^+$ − MeOH, 96.5).

Anal. Calcd for $C_{14}H_{14}Cl_2N_4O$: C, 51.69; H, 4.30; N, 17.27. Found: C, 51.66; H, 4.39; N, 17.29.

Also, the ether-insoluble solid **11** (488 mg, 50%) was identical with an authentic sample.

From 10 mmol of the indolenine, **9** (1.534 g, 100%) and **11** (977 mg, 100%) were obtained, respectively, calculated on the basis of CC.

Reaction of 2,4-Dichloro-6-methoxy-*s*-triazine with the Indolenine 3. A mixture of the *s*-triazine (980 mg, 5 mmol) and **3** (1.59 g, 10 mmol) in dry CH_3CN (2 ml) was boiled for 1 h. The solvent was removed at room temperature and the residue was extracted with anhydrous Et_2O followed by preparative TLC developed with benzene to give two main bands, which were extracted with Et_2O and crystallized from *n*-hexane, respectively. The upper band was assigned as **14** (362 mg, 24%): mp 81–82 °C; ir 1650 cm^{-1} (C=C); NMR δ 8.60–8.39 (1, m, C_7· H), 7.50–7.10 (3, m, aromatic H), 6.39 [1, d, J = 1.8 Hz, olefinic H(b)], 5.02 [1, d, J = 1.8 Hz, olefinic H(a)], 4.10 (3, s, $-OCH_3$), 1.43 [6, s, 3′,3′-$(CH_3)_2$]; *m/e* 302 ($M\cdot^+$, 20.1), 287 ($M\cdot^+ - \cdot CH_3$, 85.4).

Anal. Calcd for $C_{15}H_{15}ClN_4O$: C, 59.53; H, 4.95; N, 18.51. Found: C, 59.49; H, 4.95; N, 18.64.

The other band contained **15** (769 mg, 48%): mp 132–133 °C; ir 3410 cm^{-1} (–OH); NMR δ 8.23–8.03 (1, m, C_7· H), 7.32–7.00 (3, m, aromatic H), 6.27 (1, s, –OH), 4.02 (3, s, $-OCH_3$), 1.57 (3, s, 2′-CH_3), 1.39 and 1.22 [6, s, 3′,3′-$(CH_3)_2$]; *m/e* 320 ($M\cdot^+$, 49.7), 305 ($M\cdot^+ - \cdot CH_3$, 52.1), 304 ($M\cdot^+ - CH_4$, 38.4).

Anal. Calcd for $C_{15}H_{17}ClN_4O_2$: C, 56.16; H, 5.30; N, 17.47. Found: C, 56.42; H, 5.62; N, 17.65.

The ether-insoluble solid **11** (939 mg, 96%) was identical with an authentic sample. A band close to the baseline on TLC was also extracted with Et_2O and identified as **3** (24 mg, 3%, crude).

Acknowledgment. The authors are indebted to Professor Eugene E. van Tamelen, Stanford University, and his group for giving us the opportunity to use the facilities for this research. We also thank Dr. Roy Neville for his useful discussions of this investigation.

Registry No.—**1**, 538-75-0; **2**, 1197-48-4; **3**, 1640-39-7; **4**, 58502-52-6; **5**, 58502-53-7; **6**, 30369-82-5; **7**, 58502-54-8; **9**, 58502-55-9; **10**, 58502-56-0; **11**, 17790-92-0; **14**, 58502-57-1; **15**, 58502-58-2; CC, 108-77-0; 2,4-dichloro-6-methoxy-*s*-triazine, 3638-04-8.

References and Notes

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(6) Many *N*-acyl-3,3-di- or 2,3,3-trisubstituted 2-chloro (or other electron attracting group substituted) indolines from corresponding indolenines have been reported: "The Chemistry of Heterocyclic Compounds", Interscience, New York, N.Y., 1954, p 46, and references cited therein.
(7) The ratio was estimated on the basis of the signals of the olefinic and the hydroxy protons in the NMR spectrum. The ratio was not changed in a NMR sample tube kept for 1 week.
(8) The same manner as ref 7 for the estimation.
(9) The compound was extremely unstable and lost weight during weighing in preparation for the microanalysis owing to atmospheric hydrolysis to benzylamine hydrochloride.
(10) The calculated values for the cyanuric chloride salt, $PhCH_2{}^+N(R)=C(Cl^-)(CH_3)_2$-$C_{13}H_{13}Cl_3N_4$, are C, 47.58; H, 3.92; N, 16.89.
(11) The liquid was solidified within 30 min, mp 66–68 °C.

Ethoxycarbonylnitrene Insertion Selectivity. Photolysis of Ethyl Azidoformate in Bicyclo[4.*n*.0]alkanes and in Alkylcyclohexanes

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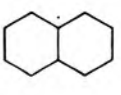
We first observed the influence of halogenated solvents in lowering the insertion selectivity of ethoxycarbonylnitrene (EtOCON) generated by the thermal decomposition of ethyl azidoformate ($EtOCON_3$) toward the C–H bonds of *cis*- and *trans*-decalins.[1] Assuming stabilization of the singlet nitrene by dichloromethane, a possible explanation is that the triplet nitrene inserts into the tertiary C–H bonds of these hydrocarbons.[2] Later, Brinkmann et al.[3] found by the CIDNP technique during the thermolysis of ethyl azidoformate in *trans*-decalin an emission signal indicating the intermediacy of a radical pair. However, the multiplicity of the reactive intermediate, i.e., whether a triplet or a singlet diradical nitrene generates ·NHCOOEt, remained an open question.



Another case concerning the same effect of the dichloromethane has been reported by Belloli et al.[4] for the thermolysis of ethyl azidoformate in *trans*-1,2-dimethylcyclohexane (TDCH). The proportion of tertiary product to other isomers

Table I. Ratio of CH/CH_2 Bonds Reactivity of Hydrocarbons toward Ethoxycarbonylnitrene[a]

Registry no.	Entry	Hydrocarbon	Thermolysis CH_2Cl_2	Thermolysis Neat	Photolysis
493-01-6	1		2.3[b]	2.9[b]	4.5
2207-01-4	2		4.0	4.4	5.0
493-02-7	3		1.3[b]	2.3[b]	3.7
6876-23-9	4		2.0	2.5[c]	3.2
4551-51-3	5		2.8[b]	3.0[b]	3.1
286-08-8	6		0.4[b]	0.5[b]	0.5
108-87-2	7		2.6	3.1	4.1

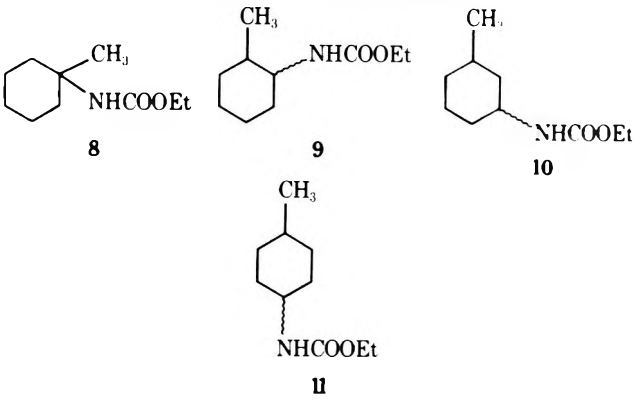
[a] The average deviation of these values is 0.15. [b] Reference 2. [c] This value is in good agreement with that found by Belloli et al. (ref 4) for the same reaction (2.4).

dropped from 38.7% for neat TDCH to 22.6% for 8.1 mol of TDCH in CH_2Cl_2.

We now report on the results obtained for the photolysis of $EtOCON_3$ (Hanovia medium-pressure 100-W lamp, room temperature, 6–8 h) in neat *cis*- and *trans*-bicyclo[4.4.0]decanes (decalins) (**1** and **3**), *cis*-bicyclo[4.3.0]nonane (hydrindane) (**5**), *cis*-bicyclo[4.1.0]heptane (norcarane) (**6**), *cis*- and *trans*-1,2-dimethylcyclohexanes (CDCH and TDCH) (**2** and **4**), and methylcyclohexane (**7**). Repeated experiments and careful integration of peak areas gave the results shown in Table I. The data clearly show that the photolysis of $EtOCON_3$ in *cis* and *trans*-decalins, in *cis*- and *trans*-1,2-dimethylcyclohexanes, and in methylcyclohexane gave an increased insertion selectivity, while no change was observed for the other substrates. The analogous behavior found for both *cis*-decalin and CDCH and *trans*-decalin and TDCH was to be expected from the similar steric situation of such pairs of hydrocarbons. An interesting point is the parallel between the solvent effect previously noted in the thermolysis and the increase in insertion selectivity found in the photolysis, namely, the same hydrocarbons which suffered solvent influence on insertion selectivity during the thermolysis gave also higher selectivity ratio in the photolysis.

On the basis of experimental evidence[5] it is commonly assumed that about 30% of ethoxycarbonylnitrene is generated in the triplet state by the photolysis of ethyl azidoformate. On account of this, the present data might give further support to our assumption that the triplet nitrene is reactive in particular cases where high stable tertiary alkyl radicals are involved in a process of hydrogen abstraction–recombination.[6] Probably the radical stability is more important than the above-mentioned steric factor. From this point of view the data concerning the thermolysis and the photolysis of $EtOCON_3$ in bicyclo[4.1.0]heptane are consistent with the low stability of the tertiary radical derived from **6**, as shown by the behavior of the radical chlorination of this hydrocarbon,[7] while the high stability of the tertiary decalyl radical is well established.[8] However, on this basis, we are unable to rationalize the behavior of bicyclo[4.3.0]nonane for which the stability of the tertiary radical is comparable. On the other hand, the high selectivity displayed by triplet methylene[9] or triplet oxygen[10] in insertion reactions on C–H bonds is well known. Nevertheless, we do not exclude the intervention of the singlet

Chart I. Tertiary and Secondary Insertion Products of EtOCON on Methylcyclohexane



diradical nitrene as recent LCAO–MO–SCF calculations[11] suggest for the reaction between EtOCON and C–H bonds.

Experimental Section

Analytical VPC was carried out by a Carlo Erba Fractovap GI gas chromatograph using an Emulphor capillary column (60 m × 0.29 mm). Infrared spectra were obtained on a Perkin-Elmer 257 Infracord instrument. ^1H NMR spectra were recorded on a Perkin-Elmer R32 90-MHz spectrometer. Mass spectra were obtained on a AEI-MS12 spectrometer at an ionization potential of 70 eV. Photolyses were carried out in a quartz vessel using a medium pressure Hanovia PCR lamp. The volume ratio of ethyl azidoformate to hydrocarbon (to dichloromethane) was 1:10 (:100). Irradiation time was 6–8 h.

Ethyl azidoformate was prepared from ethyl chloroformate and sodium azide.[12] *cis*-Bicyclo[4.1.0]heptane was obtained from WBL. Pure *cis*-bicyclo[4.3.0]nonane was obtained by spinning band distillation of commercial cis, trans mixture (Koch-Light). All other hydrocarbons are available from Fluka. The C–H insertion products (carbamates) for *cis*- and *trans*-bicyclo[4.4.0]decanes, *cis*-bicyclo[4.3.0]nonane, and *cis*-bicyclo[4.1.0]heptane were previously reported.[2] For the isomeric *cis*- and *trans*-1,2-dimethylcyclohexanes carbamates we found the same order of elution as observed by Belloli et al.[4] Identification of the eight isomeric methylcyclohexane carbamates was made by comparison of VPC retention times and spectra with those of independently synthesized compounds. The order of elution was a first peak for the tertiary C–H insertion product, followed by six partially overlapping peaks for the secondary insertion products, and finally a peak for the primary insertion product.

Ethyl *N*-(2-Methylcyclohexyl)carbamates (9). A solution of 500 mg (3.5 mmol) of *o*-toluidine hydrochloride in 5 ml of absolute ethanol was hydrogenated at 55 °C (1 atm) in the presence of 50 mg of PtO_2 Adams. The filtrate was evaporated and the residue dissolved in NaOH (2 N) and extracted with ether. To the organic layer, washed with saturated NaCl solution, 5 ml of water and, at 5 °C with stirring, 540 mg (5 mmol) of ethyl chloroformate were added. The stirring was continued for 30 min and the ether layer was separated, washed with saturated NaCl solution, dried over anhydrous sodium sulfate, and evaporated to dryness. Quantitative yield of the two isomers was obtained (74% of the shorter retention time product): ir (CCl_4) 3460 (NH) and 1730 cm^{-1} (CO); NMR (CCl_4) δ 1.25 (t, CH_3 of Et), 0.9 (d, CH_3), 3.4 (m, NCH), 4.05 (q, CH_2 of Et), 4.5 (broad, NH); *m/e* 185 (parent), 128 (base peak).

Ethyl *N*-(3-Methylcyclohexyl)carbamates (10). Two isomers (36% of the shorter retention time product) were obtained with the procedure described above starting from *m*-toluidine hydrochloride: ir (CCl_4) 3450 (NH) and 1730 cm^{-1} (CO); NMR (CCl_4) δ 1.2 (t, CH_3 of Et), 0.9 (d, CH_3), 4.0 (q, CH_2 of Et), 4.6 (broad, NH); *m/e* 185 (parent), 142 (base peak).

Ethyl *N*-(4-Methylcyclohexyl)carbamates (11). Two isomers (80% of the shorter retention time product) were obtained with the procedure described above starting from *p*-toluidine hydrochloride: ir (CCl_4) 3450 (NH) and 1730 cm^{-1} (CO); NMR (CCl_4) δ 1.25 (t, CH_3 of Et), 0.95 (d, CH_3), 4.05 (q, CH_2 of Et), 4.8 (broad, NH), 3.8 (m, NCH); *m/e* 185 (parent), 128 (base peak).

Ethyl *N*-(1-Methylcyclohexyl)carbamate (8). A mixture of 2.5 ml of glacial acetic acid, 2.28 g (0.02 mol) of 2-methylcyclohexanol (BDH), and 1.15 g of NaCN was added under stirring to a solution of 2.5 ml of 90% H_2SO_4 in 2.5 ml of glacial acetic acid over a period of 30 min. The temperature was maintained at 50–60 °C. The reaction mixture was then allowed to stand at room temperature overnight;

afterwards it was cooled and 8.5 g of ice and 11 g of NaOH in 21 ml of water were added. The mixture was then refluxed for 4 h. The cooled solution was extracted with ether. The ether layer was then extracted with 2 N HCl. The amine was extracted with ether from the water layer made alkaline. Treatment with ethyl chlorocarbonate afforded 1.95 g of carbamate: ir (CCl_4) 3450 (NH) and 1730 cm^{-1} (CO); NMR (CCl_4) δ 1.25 (t, CH_3 of Et), 1.1 (s, CH_3), 3.95 (q, CH_2 of Et), 4.25 (broad, NH); *m/e* 185 (parent), 142 (base peak).

Acknowledgment. We are grateful to the Italian Research Council (CNR), Rome, for partially supporting this work.

Registry No.—**8**, 1837-74-7; *cis*-**9**, 58486-01-4; *trans*-**9**, 58486-02-5; *cis*-**10**, 58486-03-6; *trans*-**10**, 58486-04-7; *cis*-**11**, 58486-05-8; *trans*-**11**, 58486-06-9; *o*-toluidine HCl, 636-21-5; ethyl chloroformate, 541-41-3; *m*-toluidine HCl, 638-03-9; *p*-toluidine HCl, 540-23-8; ethyl azidoformate, 817-87-8.

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Some Reactions of Chlorotrialkyl-1,3-cyclobutanediones

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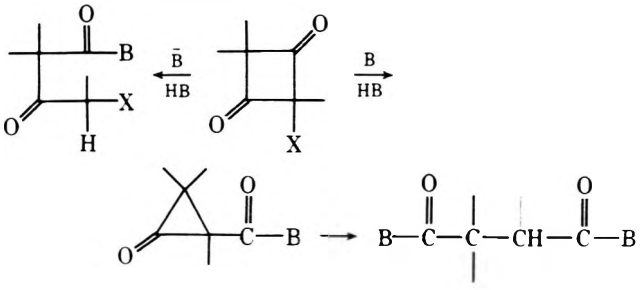
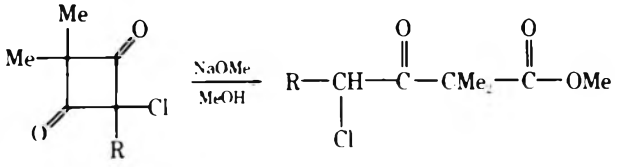
The base-catalyzed ring contraction of α-halocyclobutanones to cyclopropyl derivatives is a very useful and well-documented reaction.[1,2] Tetraalkyl-1,3-cyclobutanediones undergo ring opening reactions in the presence of base to yield β-keto esters.[3] 1,2-Cyclobutanedione has been prepared and shown to undergo ring contraction to hydroxycyclopropanecarboxylic acid.[4] In view of these considerations, the halotrialkyl-1,3-cyclobutanediones provide an interesting system for study. It would appear that such compounds could undergo



a ring contraction reaction and/or a ring opening reaction. The cyclopropanone would be expected to undergo ring opening in the presence of base to yield a succinic acid derivative. Consequently, the purpose of this paper is to investigate the reaction of chlorotrialkyl-1,3-cyclobutanediones with sodium methoxide in methanol and also to examine some chemistry of these diones as related to tetraalkylcyclobutanediones.

The chlorotrialkyl-1,3-cyclobutanediones are readily available from the mixed dimerizations of dimethylketene and alkylhaloketenes.[5] The treatment of several chlorotrialkyl-1,3-cyclobutanediones with sodium methoxide in methanol



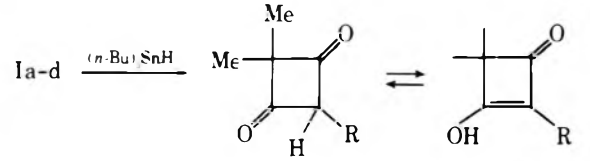
Ia, R = Me
b, R = Et
c, R = *i*-Pr

IIa, R = Me
b, R = Et
c, R = *i*-Pr

yielded the ring opened products, β-keto esters. Although two β-keto esters are possible, only the expected γ-chloro-β-keto ester was found. There was no evidence of the cyclopropanone derivative or the diester of succinic acid.

Apparently, the strain associated with the cyclopropanone ring system prohibits this ring contraction pathway from being followed. The formation of only the γ-chloro-β-keto ester is consistent with the chloro substituent stabilizing the carbanionic character in the transition state to a greater degree than the methyl substituents. The ring opening reaction of tetramethyl-1,3-cyclobutanedione requires a much longer reaction time than the chlorotrialkyl-1,3-cyclobutanedione. This further supports the stabilizing influence of the chloro substituent. The rate of the reaction decreases as the size of R increases from methyl to isopropyl as expected. When R is *tert*-butyl, ring opening does not occur; the dione is completely recovered.

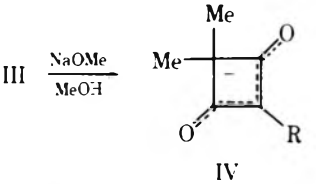
The chlorotrialkyl-1,3-cyclobutanediones (I) react with tri-*n*-butyltin hydride to yield the corresponding trialkyl-1,3-cyclobutanediones (III), which exist as the dione in the



IIIa-d

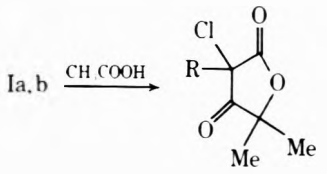
solid state, but the enol form is the predominant form in solution as evidenced by infrared. Conversion of the chlorotrialkyl-1,3-cyclobutanediones to the trialkyl-1,3-cyclobutanediones could also be accomplished by treatment with sodium borohydride in methanol.

The trialkyl-1,3-cyclobutanediones (III) did not undergo ring opening reactions. Apparently, the well-delocalized enolate, IV, is immediately produced in the basic media, and the reaction is terminated at this stage.



IV

The peracid oxidation of tetramethyl-1,3-cyclobutanedione occurs smoothly and in good yield to the expected lactone.[6,7] This Baeyer–Villiger oxidation of Ia and Ib gives the ring expansion product, V, in good yield. No other ring expansion product could be detected. The structure of V was assigned on the basis of the NMR data, i.e., the chemical shift of the geminal methyl groups in V is comparatively downfield

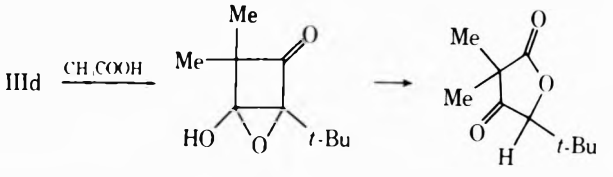


Va,b

from the chemical shift of the geminal methyl groups in Ia–d.

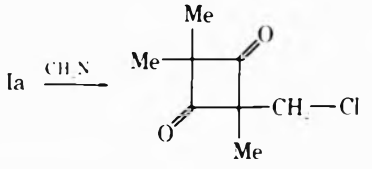
Baeyer–Villiger oxidation of Ic and Id did not occur; the diones were recovered unchanged. This is not too surprising since it is known that the C–Cl dipole effect directs attack to the R side of the molecule.[8] Apparently, when R is isopropyl and *tert*-butyl, the reaction is sterically retarded.

The Baeyer–Villiger oxidation of the trialkyl-1,3-cyclobutanediones yielded several products as evidenced by VPC analysis. The only isolated and identified product was formed from IIId. The assignment of the structure to the ring expanded VI was based on the downfield proton signal of the methinyl hydrogen in the NMR.



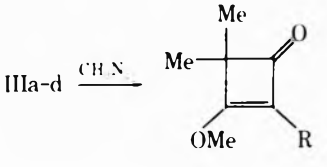
VI

Diazomethane reacts with tetramethyl-1,3-cyclobutanedione to give the ring expanded product in quantitative yield.[9] However, the reaction of diazomethane with Ia–d yields a mixture of products and nonvolatile polymeric material. The only identifiable isolated product was from Ia, and the following structure was assigned based on the NMR and mass spectrometry data.



VII

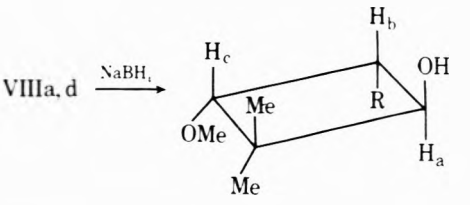
The reaction of diazomethane with trialkyl-1,3-cyclobutanediones resulted in methylation of the hydroxy group of the enolic form.



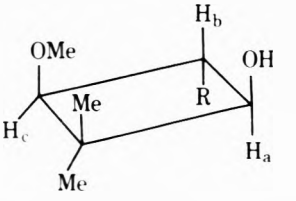
VIIIa–d

Mayr has recently reported the ring opening of cyclobutenones to vinylketenes in refluxing hexane.[10] Extended refluxing of the methoxycyclobutenones, VIII, resulted in no change. Tetraalkyl-1,3-cyclobutanediones isomerize to the corresponding 2-oxetanones in the presence of aluminum chloride.[11] This isomerization was not observed for either the chlorotrialkyl-1,3-cyclobutanediones or the trialkyl-1,3-cyclobutanediones.

The sodium borohydride reduction of the methylated trialkyl-1,3-cyclobutanediones, VIII, led to the corresponding saturated alcohols in quantitative yields. Of the four isomeric alcohols that are possible, only two were detected, and these were IX and X as evidenced by NMR analysis. When R is methyl the ratio of X/IX is 2.2, and when R is *tert*-butyl the ratio of X/IX is 0.3. When R is *tert*-butyl, the alcohol IXd revealed H_a (d, 1 H, 3.76 ppm, J_{a-b} trans = 7 Hz) and H_c (d, 1 H, 3.47 ppm, J_{b-c} cis = 10 Mz). Conversely, the isomer Xd (the minor isomer) revealed H_a (d, 1 H, 3.11 ppm, J_{a-b} trans = 7 Hz) and H_c (d, 1 H, 2.76 ppm, J_{b-c} trans = 7 Hz). In IX, H_a is cis to the methoxy, and H_c is cis to the hydroxy group; consequently, the chemical shifts of these hydrogens are comparatively downfield relative to X in which H_a is trans to the methoxy and H_c is trans to the hydroxy group.



IXa,d



Xa,d

Experimental Section

^{1}H NMR spectra were recorded on a Jeolco PS-100 NMR spectrometer employing tetramethylsilane as an internal standard. VPC was performed on an F & M Scientific Model 700 gas chromatograph with 10 ft × 0.25 in. columns packed with 10% SE-30 and Carbowax 20M on acid-washed Chromosorb W (80/100). The chlorotrialkyl-1,3-cyclobutanediones were prepared as previously described.[5]

General Procedure for Treatment of Chlorotrialkyl-1,3-cyclobutanediones with Sodium Methoxide in Methanol. To 50 ml of methanol containing 0.5 g of sodium methoxide was added 0.015 mol of I, and the solution was heated to reflux. The reaction was monitored by VPC as a 2- to 7-day refluxing time was required for consumption of I. Upon cooling, the reaction solution was concentrated on a rotatory evaporator, neutralized with dilute acid in an ice bath, and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, the solvent removed, and the residue vacuum distilled.

Methyl 4-Chloro-2,2-dimethyl-3-ketopentanoate (IIa). The reaction was complete in 2 days as evidenced by VPC, and the ester was obtained in 82% yield: bp 42–44 °C (0.05 mm); ir 1718 and 1748 cm^{-1}; NMR δ 1.40 (s, 3 H), 1.49 (s, 3 H), 1.58 (d, 3 H), 3.72 (s, 3 H), and 4.65 (q, 1 H); mass spectrum parent peak at *m/e* 192.

Methyl 4-Chloro-2,2-dimethyl-3-ketohexanoate (IIb). This keto ester was obtained after 5 days of refluxing in 75% yield: bp 50–52 °C (0.05 mm); ir 1718 and 1748 cm^{-1}; NMR δ 0.90 (t, 3 H), 1.26 (s, 3 H), 1.36 (s, 3 H), 1.80 (m, 2 H), 3.52 (s, 3 H), and 4.12 (t, 1 H); mass spectrum parent peak at *m/e* 206.

Methyl 4-Chloro-2,2,5-trimethyl-3-ketohexanoate (IIc). Some dione remained after 7 days, but the keto ester was obtained in a 60% yield: bp 59–60 °C (0.05 mm); ir 1718 and 1748 cm^{-1}; NMR δ 1.0 (2 d, 6 H), 1.44 (s, 3 H), 1.52 (s, 3 H), 2.40 (m, 1 H), 3.83 (s, 3 H), and 4.40 (d, 1 H).

Anal. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.71. Found: C, 54.65; H, 7.80.

General Procedure for Conversion of Chlorotrialkyl-1,3-cyclobutanediones to Trialkyl-1,3-cyclobutanediones. To 0.1 mol of I in 150 ml of cold hexane containing 0.1 g of azobisisobutyronitrile was added dropwise 0.12 mol of freshly distilled tri-*n*-butyltin hydride. This mixture was stirred in the ice bath for an additional 2 h. The crude product was separated from the reaction solution by filtration, washed with ether, and recrystallized from methanol.

Trimethyl-1,3-cyclobutanedione (IIIa). An 80% yield of this dione was obtained: mp 165–166 °C; ir (Me_2SO) 1620, 1753, and 3444 cm^{-1}; NMR (Me_2SO) δ 1.12 (s, 6 H), 1.40 (s, 3 H), and 2.52 (s, 1 H); mass spectrum parent peak at *m/e* 126.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.66; H, 7.94. Found: C, 66.82; H, 8.46.

4-Ethyl-2,2-dimethyl-1,3-cyclobutanedione (IIIb) was obtained in 85% yield: mp 143–145 °C; ir (Me_2SO) 1612, 1739, and 3444 cm^{-1}; ir (KBr) 1739 cm^{-1}; NMR (Me_2SO) δ 1.02 (t, 3 H), 1.16 (s, 6 H), 1.92 (q, 2 H), and 2.58 (s, 1 H); mass spectrum parent peak at *m/e* 140.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 67.97; H, 8.76.

2,2-Dimethyl-4-isopropyl-1,3-cyclobutanedione (IIIc) was obtained in 80% yield: mp 138–140 °C; ir (Me_2SO) 1612, 1742, and 3444 cm^{-1}; ir (KBr) 1759 cm^{-1}; NMR (Me_2SO) δ 0.98 (d, 6 H), 1.06 (s, 6 H), 2.24 (septet, 1 H), and 2.44 (s, 1 H); mass spectrum parent peak at *m/e* 154.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 70.03; H, 9.54.

4-*tert*-Butyl-2,2-dimethyl-1,3-cyclobutanedione (IIId) was obtained in 90% yield: mp 217 °C; ir (Me_2SO) 1633, 1739, and 3444 cm^{-1}; ir (KBr) 1724 cm^{-1}; NMR (Me_2SO) δ 1.12 (s, 15 H), 2.54 (s, 1 H); mass spectrum parent peak at *m/e* 8.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 71.66; H, 9.70.

General Procedure for Baeyer–Villiger Oxidation. The peroxyacetic acid was prepared by a standard procedure.[12] To 50 ml of $CHCl_3$ containing 0.015 mol of I or III was added dropwise at room temperature 0.05 mol of peracetic acid. The solution was stirred and the reaction monitored by VPC. After the disappearance of all the dione, the organic layer was separated and washed with dilute sodium carbonate solution and then dried over magnesium sulfate. The $CHCl_3$ was removed under reduced pressure and the β-keto-γ-lactone distilled.

α-Chloro-α,γ-dimethyl-β-keto-γ-valerolactone (Va). This lactone was obtained in 70% yield at 53–56 °C (0.05 mm): ir 1770 and 1809 cm^{-1}; NMR δ 1.52 (s, 3 H), 1.84 (s, 6 H); mass spectrum parent peak at *m/e* 176.

Anal. Calcd for $C_7H_9ClO_3$: C, 47.60; H, 5.14. Found: C, 47.33; H, 5.01.

α-Chloro-α-ethyl-γ-methyl-γ-valerolactone (Vb). This lactone was distilled at 61–63 °C (0.05 mm) in 55% yield: ir 1770 and 1809 cm^{-1}; NMR δ 0.99 (t, 3 H), 1.56 (s, 3 H), 1.72 (s, 3 H), 2.18 (q, 2 H); mass spectrum parent peak *m/e* 190.

Anal. Calcd for $C_8H_{11}ClO_3$: C, 50.40; H, 5.82. Found: C, 50.79; H, 5.62.

α,α,δ,δ-Tetramethyl-β-keto-γ-caprolactone (VI) was obtained in 15% yield at 66–67 °C (0.05 mm): ir 1739 and 1802 cm^{-1}; NMR δ 1.06 (s, 9 H), 1.20 (s, 3 H), 1.26 (s, 3 H), and 4.24 (s, 1 H); mass spectrum parent peak at *m/e* 184.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.69. Found: C, 65.32; H, 8.99.

General Procedure for Diazomethane Reaction with Cyclobutanediones. The diazomethane was prepared by a standard procedure.[13] To 0.01 mol of I or III in 50 ml of ether was added 0.03 mol of diazomethane in ether at petroleum ether–dry ice temperature. Upon warming to room temperature, the reaction solution was stirred for 3 days. The solvent was removed under reduced pressure and the product vacuum distilled.

4-Chloromethyl-2,2,4-trimethyl-1,3-cyclobutanedione (VII). This dione was distilled at 44–46 °C (0.025 mm) in 20% yield: ir 1770 cm^{-1}; NMR δ 1.36 (s, 6 H), 2.00 (s, 3 H), and 4.24 (s, 2 H); mass spectrum parent peak at *m/e* 174.

3-Methoxy-2,2,4-trimethylcyclobutenone (VIIIa). An 87% yield was obtained at 38–39 °C (0.05 mm): ir 1616 and 1750 cm^{-1}; NMR δ 1.11 (s, 6 H), 1.60 (s, 3 H), and 4.11 (s, 3 H); mass spectrum parent peak at *m/e* 140.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 67.94; H, 8.74.

4-Ethyl-3-methoxy-2,2-dimethylcyclobutenone (VIIIb). An 85% yield was obtained at 45–47 °C (0.05 mm): ir 1616 and 1750 cm^{-1}; NMR δ 1.14 (s, 6 H), 1.40 (t, 3 H), 2.20 (q, 2 H), and 3.94 (s, 3 H); mass spectrum parent peak at *m/e* 154.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.02; H, 9.09. Found: C, 69.82; H, 9.11.

3-Methoxy-2,2-dimethyl-4-isopropylcyclobutenone (VIIIc). This compound was obtained at 52–54 °C (0.05 mm) in 80% yield: ir 1616 and 1750 cm^{-1}; NMR δ 0.92 (s, 6 H), 1.04 (s, 6 H), 2.28 (s, 1 H), and 3.96 (s, 3 H); mass spectrum parent peak *m/e* 168.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.19; H, 9.99.

4-*tert*-Butyl-3-methoxy-2,2-dimethylcyclobutenone (VIIId). A 90% yield was obtained at 45–47 °C (0.025 mm): ir 1626 and 1752 cm^{-1}; NMR δ 1.1 (s, 9 H), 1.3 (s, 6 H), and 4.0 (s, 3 H); mass spectrum parent peak *m/e* 182.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.89. Found: C, 71.81; H, 9.97.

General Procedure for Sodium Borohydride Reduction. To a stirred solution of 0.015 mol of VIII in 100 ml of methanol was slowly added sodium borohydride until the reduction was complete as evidenced by VPC. The solvent was removed and the saturated alcohol vacuum distilled.

3-Methoxy-2,2,4-trimethylcyclobutanol (Xa). This alcohol was distilled at 35–37 °C (0.025 mm) in nearly quantitative yield: ir 3334 cm^{-1}; NMR δ 0.09 (s, 3 H), 1.08 (s, 3 H), 1.12 (s, 3 H), 1.78 (q, 1 H), 2.41 (s, 1 H), 2.54 (d, 1 H, J_{trans} = 7 Hz), and 2.82 (d, 1 H, J_{trans} = 7 Hz).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.84; H, 11.29.

4-*tert*-Butyl-3-methoxy-2,2-dimethylcyclobutanol (IXd). This alcohol was obtained at 62–63 °C (0.05 mm) in quantitative yield: ir 3334 cm^{-1}; NMR δ 0.96 (s, 9 H), 0.98 (s, 3 H), 1.04 (s, 3 H), 1.64 (s, 1 H), 1.90 (dd, 1 H), 3.22 (s, 3 H), 3.47 (d, 1 H, J_{cis} = 10 Hz), and 3.76 (d, 1 H, J_{trans} = 7 Hz).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.86; H, 11.83. Found: C, 71.22; H, 11.97.

Registry No.—Ia, 56513-93-0; Ib, 56513-92-9; Ic, 56513-95-2; Id, 56513-91-8; IIa, 58548-55-3; IIb, 58548-56-4; IIc, 56513-99-6; IIIa, 58548-57-5; IIIb, 58548-58-6; IIIc, 58548-59-7; IIId, 58548-60-0; Va, 58548-61-1; Vb, 58548-62-2; VI, 58548-63-3; VII, 58548-64-4; VIIIa, 13085-31-3; VIIIb, 58548-65-5; VIIIc, 58548-66-6; VIIId, 58548-67-7; IXd, 58548-68-8; Xa, 58548-69-9.

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Photochemistry of Diphenylcyclopropanecarboxylic Acid Derivatives

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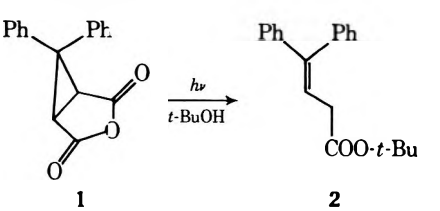
Although the photoextrusion of carbenes by arylcyclopropanes is a general reaction, the importance of this process relative to others available to excited cyclopropanes is highly structure dependent.[1] We wish to report here our observations concerning this process in two diphenylcyclopropanecarboxylic acid derivatives.

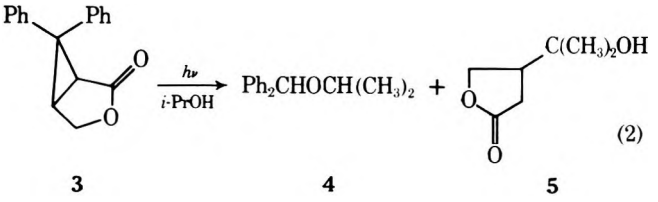
Results and Discussion

Irradiation of the anhydride 1[2] in *tert*-butyl alcohol with Vycor-filtered light for 4 h afforded (1,1-dimethyl)ethyl 4,4-diphenylbut-3-enoate (2) in 57% yield at 10% conversion. No (1,1-dimethyl)ethylbenzhydryl ether[3] could be detected. In contrast to this, a similar irradiation of the lactone 3 in isopropyl alcohol produced benzhydryl isopropyl ether (4) in 80% yield and the hydroxy lactone 5 in 75% yield at 11% conversion. In each case sensitization with acetone using Corex-filtered light was unsuccessful. The structures of the photoproducts were confirmed by comparison with independently synthesized, previously reported materials.[3–5]



(1)

1 2



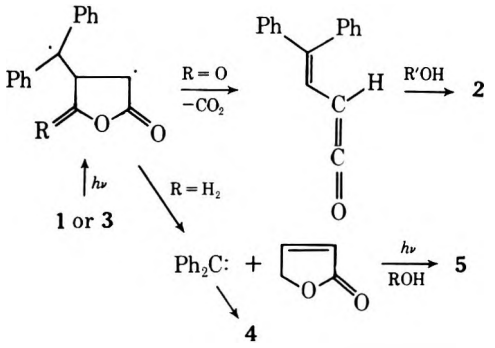
(2)

3 4 5

Both of these reactions can be rationalized in terms of cyclopropane bond homolysis to produce trimethylene diradicals.[1,6] In the case of the anhydride, cycloelimination of carbon dioxide would then lead to the formation of an unsaturated ketene which should capture solvent to give the observed product. This is depicted in Scheme I.

The diradical derivable from 3 cannot eliminate CO_2 in the same fashion and thus may fragment to diphenylcarbene and the unsaturated lactone. This olefin is known[5] to add isopropyl alcohol photochemically in the manner depicted in Scheme I.

Scheme I



It should be noted that the evidence presented here does not require the intermediacy of a diradical. Hixson[7] has shown that a cyclopropane closely related to those described here fragments stereospecifically to produce the diphenylcarbene and an olefin in a process that, as in these reactions, originates only from the singlet excited state.

Experimental Section

General. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian Associates T-60 instrument with tetramethylsilane as the internal standard. Irradiations were conducted using a 450-W Hanovia lamp in a quartz immersion well. Irradiation solutions were deoxygenated by bubbling nitrogen through them for 1 h before and then during irradiation. Isopropyl alcohol was distilled from magnesium just before use. *tert*-Butyl alcohol was distilled from potassium.

Irradiation of 6,6-Diphenyl-3-oxabicyclo[3.1.0]hexane-2,4-dione (1). A solution of 284 mg (1.07 mmol) of 1[2] in 330 ml of *tert*-butyl alcohol was irradiated for 4 h using a Vycor filter. After solvent removal the NMR spectrum of the photomixture indicated that the major component of the mixture was starting material, but that there was an additional absorption signal at δ 3.07. This material was dissolved in 100 ml of ether, stirred with 100 ml of water, and the organic layer washed with 10% sodium carbonate solution. The ether solution was dried and the solvent removed. The residue was chromatographed on a 2.5 × 190 cm column slurry packed in hexane; 50-ml fractions were collected. Elution was accomplished with 250 ml of hexane and then 1 l. each of 5 and 10% ether–hexane. Fractions 27–34 contained 25 mg of a yellow oil. Attempted crystallization of this oil from chloroform–hexane afforded 18 mg (57% based on recovered starting material) of a clear oil. This material was identified as (1,1-dimethyl)ethyl 4,4-diphenylbut-3-enoate by comparison with the authentic ester synthesized from the known acid.[4] The photoproduct ester was dissolved in cyclohexane containing several drops of sulfuric acid and a white precipitate formed in several minutes. This solid was recrystallized from cyclohexane to afford 13 mg of 4,4-diphenylbut-3-enoic acid, mp 116–117 °C, mmp with authentic[4] acid 116–118 °C (lit.[4] mp 114–115 °C). The NMR spectrum ($CDCl_3$) is δ 9.8 (br, 1 H, COOH), 7.1–6.9 (m, 10 H), 5.97 (triplet, 1 H, J = 6 Hz), 3.07 (doublet, 2 H, J = 6 Hz). The spectrum of the *tert*-butyl ester was identical with the exception of the absence of the acid proton resonance and the presence of the *tert*-butyl group absorption at δ 1.43 (singlet, 9 H). Acidification of the sodium carbonate wash afforded 271 mg of a mixture of the *cis*- and *trans*-3,3-diphenyl-1,2-cyclopropanedicarboxylic acids.[2] A similar irradiation of 1 using 10.0 ml of acetone (0.136 mol) as a sensitizer and a Corex light filter gave no detectable reaction in a 12-h irradiation.

6,6-Diphenyl-3-oxabicyclo[3.1.0]hexan-2-one (3). A solution of 1.80 g (9.28 mmol) of diphenyldiazomethane[8] in 100 ml of dry benzene was added dropwise over 0.5 h to a solution of 2.00 g (23.8 mmol) of 2 (5*H*)-furanone[9] in 100 ml of dry benzene at room temperature. This material was heated at reflux for 4 h and the solvent removed in vacuo. The oily product mixture was chromatographed on a 2.5 × 87.5 cm column of Florisil slurry packed in hexane; 50-ml fractions were collected. Elution was with 500 ml of hexane and 500-ml portions of 2, 4, 8, and 15% ether–hexane. Fractions 23–25 contained 610 mg of an oil. Crystallization from ether–hexane afforded 458 mg (20%) of 3, mp 136–137 °C. Spectral data were uv (CH_3OH) 274 nm (ϵ 34), 268 (59), 261 (60), 254 (49); NMR ($CDCl_3$) δ 2.80 (multiplet, 2 H), 4.25 (m, 2 H), 7.1 (m, 10 H); MS (50 ev) *m/e* (rel intensity) 250 (31) (M^+), 205 (100), 165 (68); ir (KBr) 1775 (sh), 1750 (sh), 1195, 700 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.88; H, 5.69.

Irradiation of 6,6-Diphenyl-3-oxabicyclo[3.1.0]hexan-2-one (3). A solution of 301 mg (1.20 mmol) of 3 in 330 ml of isopropyl alcohol was irradiated for 4 h using a Vycor filter. After solvent removal most of the starting material was crystallized from ether–hexane, 268 mg, mp 135–137 °C. The residue was then separated by gas chromatography (156 °C, 20% SE-30 on firebrick in a 5 ft × 0.25 in. column, flow rate 60 ml He/min) to give 24 mg of isopropyl benzhydryl ether (4) (retention time 2.7 min) and 15 mg of 4-(1′-hydroxy-1′-methylethyl)-4,5-dihydro-2(3*H*)-furanone (5) (retention time 21 min). The identities of these materials were confirmed by the superimposability of their ir and NMR spectra upon those of independently synthesized materials. The ether 4 was made by a standard method[10] and the hydroxy lactone prepared by the irradiation of 2(5*H*)-furanone[9] as reported by Ohga and Matsuo.[5] A similar irradiation of 3 in which 10 ml of the solvent was replaced by acetone as a sensitizer afforded no reaction after 12 h of irradiation.

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Registry No.—1, 26844-85-9; 2, 58540-89-9; 2 free acid, 7498-88-6; 3, 58540-90-2; diphenyldiazomethane, 883-40-9; 2(5*H*)-furanone, 497-23-1.

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A Phosgeneless Synthesis of Diaryl Carbonates

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The production of diaryl carbonates most often involves at some point the use of extremely toxic phosgene. In this

paper we report the synthesis of carbonates without the use of phosgene by employing esters of dichloroacetic acid. The overall reaction is shown in reaction 1 for phenyl dichloroacetate.

$$\underset{\mathbf{1}}{C_6H_5—O—CO—CHCl_2} + NaH \longrightarrow \underset{\mathbf{2}}{C_6H_5—OCOOC_6H_5} + H_2 \quad (1)$$

This reaction is unusual in that it results in an oxidative cleavage of C–C bonds apparently brought about by sodium hydride. The yield of diphenyl carbonate was modest, 35–70%, and was accompanied by formation of tar and phenol along with dichloroacetic acid on water workup of the reaction mixture.

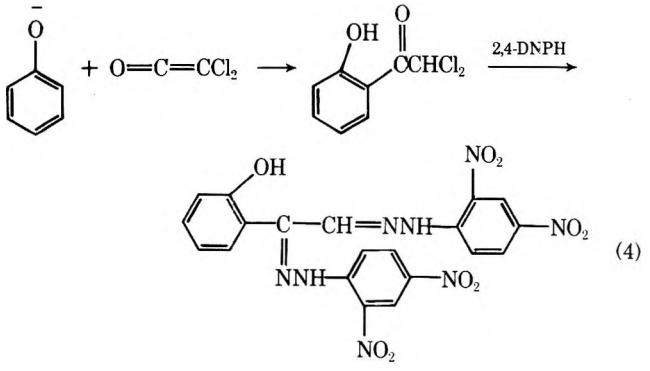
A reasonable mechanism would involve attack of phenoxide, as in eq 2, on the carbonyl.

$$C_6H_5—O—\overset{O}{\overset{\|}{C}}—CHCl_2 + \bar{O}—C_6H_5 \longrightarrow \underset{\mathbf{3}}{C_6H_5—O—\overset{\bar{O}}{\overset{|}{C}}(O—C_6H_5)—CHCl_2} \quad (2)$$

This attack would be followed by expulsion of $CHCl_2$ from **3** or a concerted expulsion of Cl^- and :CHCl such as has been reported[2] in the reaction of dichloroacetophenone with *tert*-butoxide. Indeed, it was found that phenoxide ion cleaved the phenyl dichloroacetate to give diphenyl carbonate in 60% yield, thus implicating phenoxide as in reaction 2. With carefully purified phenyl dichloroacetate, having literature[3] values for physical constants, and containing no detectable phenol by GC, reaction 1 gave diphenyl carbonate in yields up to 71%, indicating that the ester must be the source of the phenolate ion. Reaction 3 shows that phenolate ion could be plausibly generated by expulsion of dichloroketene from the ester after abstraction of a proton (reaction 3).

$$1 + NaH \longrightarrow \underset{\mathbf{4}}{C_6H_5O—COCCl_2} \longrightarrow C_6H_5O + Cl_2C=C=O \quad (3)$$

Attempts to trap dichloroketene with cyclohexene[6] or cyclopentadiene[7] were not successful. However, from the reaction mixture with cyclohexene a very small amount of a ketone having $\nu_{C=O}$ at 1655 cm^{-1} and giving a 2,4-DNP osazone derivative consistent with the reactions in eq 4 was isolated. This



(4)

2,4-dinitrophenylosazone was identical with one obtained from an authentic 2-hydroxy-α,α-dichloroacetophenone prepared by a Fries rearrangement of the phenyl dichloroacetate.[4] Such osazone formation is typical behavior for α,α-dichloroacetophenones and has long been known.[5] The failure to trap dichloroketene with dienes or 2,3-dimethyl-2-butene could be considered a serious argument against this mechanism. However, as we show below, from consideration of the mass balance in alternate mechanisms, dichloroketene expulsion must be fairly important; and the isolation of this ketone and the vinyl dichloroacetate ester described below must indicate generation of dichloroketene. Apparently dichloroketene is reluctant to attack even a very electron-rich aromatic ring such as phenolate ion and instead undergoes alternate fates expected of it.

The source of phenolate ion could also be considered a path such as reaction 5. This type of derivative of dichloroacetic

$$C_6H_5O\bar{C}OCCl_2 + 1 \longrightarrow \underset{\mathbf{5}}{C_6H_5OC(O—COCHCl_2)=CCl_2} + C_6H_5\bar{O} \quad (5)$$

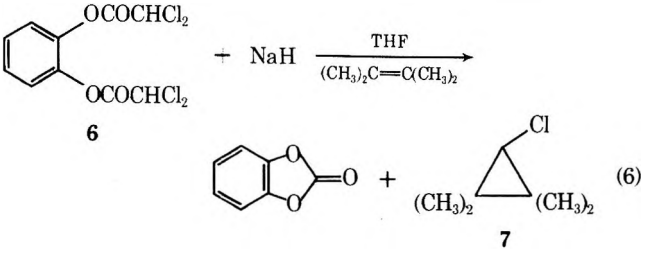
acid was found by Lavanish when he treated excess dichloroacetyl chloride with triethylamine.[8] Such behavior toward enolate ions seems to be typical of haloketenes.[9]

When 1 was treated with one-half stoichiometric amounts of sodium hydride in THF and the solvent removed, there was obtained an oily solid which had two strong ir bands at 1780 and 1640 cm^{-1}. These bands were attributed to the carbonyl and the C=C bond in **5** in the reaction mixture. Attempts to distill this mixture led to gas evolution, and the only distillable materials obtained were phenol, starting ester, and a trace of diphenyl carbonate. Apparently **5** decomposes with expulsion of dichloroketene to give starting ester.

A chromatographic attempt was made to isolate compound **5** by chromatography on silica gel. After elution of all the reaction mixture components (see Experimental Section), a band of organic material remained at the top of the column. When this was eluted with acetone an oily semisolid was obtained which had ir bands at 1770–1790 cm^{-1} and a band at 1640 cm^{-1} and NMR signals at δ 6.05 and 5.90 ppm and a multiplet at 7.33 ppm. The signals at 6.05 and 7.33 ppm are due to the presence of starting ester, as was confirmed from examination of the infrared spectrum (see Experimental Section). The signal at 5.90 ppm we attribute to the presence of compound **5**. Furthermore, at the time of isolation the 6.05/5.90 ratio was 9/8, but in 3 h it had risen to 6.05/5.90 = 9/4. These data are consistent with the postulate that **5** is unstable relative to starting ester and dichloroketene. Reinforcement for this view comes from the realization that the starting ester was removed from the chromatography column in the second fraction and the material examined here was removed in the 12–16 fraction.

Reaction 5 cannot be solely responsible for the generation of phenolate ion because it would require 3 mol of ester to produce 1 mol of diphenyl carbonate. This would make our yields in the neighborhood of 110%. This means that, in spite of the failure of dienes to trap it, dichloroketene must be expelled in the formation of phenolate ion. The dichloroketene is then trapped by phenolate ion as o-hydroxydichloroacetophenone, and as **5** by the enolate **4**. Apparently in the presence of enolate ions this is the preferred fate for dichloroketene rather than addition to double bonds.

Following an unsuccessful attempt to trap monochlorocarbene and/or chloroform from phenyl dichloroacetate we sought to trap chlorocarbene from the bisdichloroacetate ester of catechol (eq 6) in the presence of 2,3-dimethyl-2-butene. This procedure gave low yields of the alkene–halocarbene adduct **7** as could be shown by observing NMR signals at



6 (6)

7

0.9–1.3 ppm. The cyclopropane **7** is known to display a sharply defined doublet centered at 1.25 ppm, due to chemically shifted methyl groups, and a sharp singlet at 2.70 ppm. Both of these signals are observable in the reaction mixture from reaction 7. Further evidence for the presence of **7** was found by observing a GC retention time (see Experimental Section) identical with authentic **7**.

In view of the failure to trap methylene chloride, even with phenol in the reaction mixture, we ascribe the appearance of chlorocarbene to a concerted expulsion of chloride and chlorocarbene from the intermediate ion **3** in reaction 2. This is quite consistent with the known behavior of dichloroacetophenone[2] and contrasting with haloform cleavages observed in trihalogenated esters.[11]

The reaction of bisdichloroacetate catechol ester, **6**, with sodium hydride in THF led to a smooth production of *o*-phenylene carbonate in 60–70% yield. The material obtained was identical with an authentic sample prepared by distillation of o-hydroxyphenylethyl carbonate.[12]

The synthetic usefulness of the reaction was explored briefly with the 3,5-dimethylphenol ester and the *p*-bromophenyl ester, which gave yields of 41.5 and 54%, respectively.

Experimental Section

Instrumental. All infrared spectra were measured on a Perkin-Elmer Model 700 spectrophotometer; NMR spectra were obtained on a Varian EM 360 and melting points with a Mel-Temp block, and they are uncorrected. Gas chromatography was performed on a Varian Model 920 with columns as noted. Elemental analysis was performed by Galbraith Laboratories.

Phenyl Dichloroacetate (1). This compound was made by allowing phenol and dichloroacetyl chloride to react using triethylamine as an acid scavenger. Distillation followed by recrystallization from petroleum ether–ether gave solid white crystals, mp 46–48 °C (lit.[2] 48 °C). Gas chromatography on a 20 ft × 0.375 in. SE-30 on 30/60 Chromosorb W showed 99+% purity.

Reaction of Phenyl Dichloroacetate with Sodium Hydride. In a typical procedure a three-necked 250-ml flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser was charged with 5.0 g of sodium hydride (50% dispersion in mineral oil). This was washed three times with 25 ml of dry benzene, then covered with 50 ml of dry tetrahydrofuran and 20 g (0.092 mol) of the phenyl dichloroacetate in 25 ml of dry THF was added slowly under N_2 with vigorous stirring. A lively evolution of hydrogen ensued and the solution turned red, then brown and began to reflux gently. When gas evolution ceased, the flask was stirred for 0.5 h further. Then the brown solution was poured into 300 ml of 3 N hydrochloric acid, immediately extracted with three 100-ml portions of dichloromethane, and dried over magnesium sulfate. Solvent removal left a red oil which was picked up in methylene chloride and washed with 10% sodium bicarbonate until the aqueous layer was clear. Distillation of this oil gave, after a leading fraction containing 2.8 g of phenol and one containing 1.68 g of ester, 7.2 g of diphenyl carbonate. This represents a yield of 70.8% based on 2 mol of ester consumed per mole of carbonate produced.

Catechol Bis(dichloroacetate) (6). This compound was prepared by the reaction of catechol with dichloroacetyl chloride. Typically 11.0 g (0.1 mol) of catechol was dissolved in 200 ml of benzene and 15 ml of dry diethyl ether in a three-necked mechanically stirred 1-l. flask equipped as for phenyl dichloroacetate. To this mixture 29.7 g (0.2 mol) of dichloroacetyl chloride was added and stirring was begun. A solution of 20.2 g (0.2 mol) of triethylamine in 100 ml of dry benzene was added dropwise over a 2-h period and stirring was prolonged for an additional 1 h after addition was complete.

Filtration of the suspended salt after this period gave only 8.5 g of amine salt. Subsequently the organic filtrate was washed with two 150-ml portions of 4 N hydrochloric acid and with three 100-ml portions of water. After drying over $MgSO_4$ and solvent removal, distillation (100–110 °C, 0.5 Torr) gave a solid, mp 64.5–66 °C, which was the diester, and a liquid which was the monoester (bp 70–75 °C, 0.55 Torr). The yield of solid was 65%, and the liquid was 11.5%. The solid diester was characterized by absence of ν_{OH} at 3600–3300 cm^{-1} and presence of a strong $\nu_{C=O}$ at 1770 cm^{-1} and ν_{C-O} at 1138 cm^{-1} (strong). The NMR spectrum ($CDCl_3$, vs. Me_4Si) had two strong singlets at δ 6.11 (2 H) and 7.33 (4 H).

Anal. Calcd for $C_{10}H_6O_4Cl_4$: C, 36.18; H, 1.82. Found: C, 36.15; H, 1.86.

Reaction of Catechol Bis(dichloroacetate) with Sodium Hydride. A 3.3-g (0.01 mol) sample of this diester was treated with 0.48 g (0.01 mol) of NaH in a 50% oil dispersion as described for phenyl dichloroacetate. An immediate reaction occurred which consumed the NaH in 1 min. The solution was stirred overnight and worked up with hydrochloric acid as before. The organic layer after drying and solvent removal gave 1.18 g of a solid, mp 119–120 °C, after recrystallization from ether, 60% yield. This material was identical in infrared spectroscopy [$\nu_{C=O}$ at 1780 (broad) and 1850 cm^{-1} (sh)],[13] and NMR spectroscopy (signal at δ 7.22 ppm, singlet), and physical properties to a sample of o-phenylene carbonate made by distillation of o-hydroxyphenylethyl carbonate.[12] The NMR of the authentic material showed complete absence of signals besides a singlet at δ 7.22.

When this reaction was run in the presence of 5.0 g of 2,3-dimethyl-2-butene and worked up as recorded above, the NMR spectrum in $CDCl_3$ of the reaction mixture showed signals due to chemically shifted methyl groups centered at δ 1.25 (doublet) and a sharp singlet at 2.70 ppm. These signals were similar to signals obtained from an authentic sample of **7** obtained by the method of Closs[10] (−5 °C, slow addition of butyllithium to a CH_2Cl_2 solution of 2,3-dimethyl-2-butene). Gas chromatography of the reaction mixture after removal of most of the tetrahydrofuran by distillation showed a peak at 8.6-min retention time on a 20 ft × 0.375 in. 15% SE-30 on 30/60 Chromosorb W column (column temperature 132 °C, He flow 80 ml/min). This was the identical retention time with that of the authentic sample under identical conditions.

***o*-Hydroxy-α,α-dichloroacetophenone.** This ketone was prepared by a Fries rearrangement of phenyl dichloroacetate as outlined in ref 4. There was obtained a 50% yield of a colorless to pale yellow liquid on distillation (bp 65–72 °C, 0.1 Torr)[7] which gave a 2,4-dinitrophenylosazone on warming with 2,4-DNPH in sulfuric acid–ethanol, mp 263–265 °C.

Anal. Calcd for $C_{20}H_{14}N_8O_9$: C, 47.07; H, 2.76; N, 21.95. Found: C, 46.92; H, 2.61; N, 21.86.

Trapping Experiment with Cyclohexene. A sample of 2.2 g of 50% sodium hydride in oil was washed with three 50-ml portions of dry benzene, then covered with 50 ml of dry cyclohexene and cooled to 0 to −5 °C, with ice–salt water and stirred vigorously as 20 g (0.0922 mol) of phenyl dichloroacetate was added, in 120 ml of cyclohexene, over a period of 0.5 h. After stirring for an additional 1 h, the reaction was quenched with water, and the organic phase separated and distilled. The second, third, and fourth fractions contained a ketone (bp 45–50 °C, 0.01 Torr) which gave a 2,4-DNP osazone derivative, mp 258–261 °C, ir $\nu_{C=O}$ 1650–1660 cm^{-1}.

Anal. Calcd for $C_{20}H_{14}N_8O_9$: C, 47.07; H, 2.76; N, 21.95. Found: C, 46.63; H, 3.10; N, 21.96.

The yield was less than 1% of the theoretical for this ketone.

These data are essentially those of the authentic ketone obtained from Fries rearrangement of phenyl dichloroacetate.

Isolation of Compound 5. To a 10-g (0.046 mol) sample of phenyl dichloroacetate in 100 ml of THF was added 1.0 g (0.023 mol) of sodium hydride washed free of oil. This mixture was allowed to stir for 2 h, and the solvent was removed after this time. The reaction mixture displayed a broad carbonyl band from 1790 to 1775 cm^{-1} and a medium-strong band at 1640 cm^{-1}. Distillation gave a fraction at 65–87 °C (2.0 Torr) which was mostly starting material. At 99–118 °C at 0.4–1.2 Torr three fractions were obtained along with gas evolution; these fractions were also all starting material. Finally, at 124–180 °C along with gas evolution there was obtained still another fraction of mostly starting ester. The material giving the 1640-cm^{-1} band was not obtained in this distillation although much gas evolution, presumably dichloroketene, occurred.

This experiment was repeated using 22 g of ester and 2.18 g of sodium hydride. A 3.5-g sample of the reaction mixture was chromatographed on 60–200 mesh silica gel to obtain 2.02 g of starting ester in the first five fractions (ether–50% petroleum ether). The sixth and seventh fractions (60% ether–petroleum ether) contained 25–30 mg of a red oil leaving $\nu_{C=O}$ at 1650 cm^{-1} and ν_{OH} at 3400 cm^{-1} (presumed to be the hydroxyacetophenone of reaction 4). In the 12th through 16th fractions (40% acetone–100% acetone, ethyl acetate) there was obtained an oily semisolid having $\nu_{C=O}$ at 1770 and 1640 cm^{-1}. The 1770-cm^{-1} band had a shoulder at 1780–1785 cm^{-1}. The NMR spectrum had signals at δ 6.05 (singlet) and 5.90 (singlet) (ratio of 9:8), as well as an aromatic multiplet at 7.3–7.1 ppm. After standing for 3 h, the upfield singlet diminished and the 6.05/5.90 ratio was 9.8/4.0.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—1, 10565-20-5; 2, 102-09-0; 5, 58462-98-9; 6, 58462-99-0; 6 monoester analogue, 58463-00-6; 7, 14123-41-2; catechol, 120-80-9; dichloroacetyl chloride, 79-36-7; o-phenylene carbonate, 2171-74-6; o-hydroxy-α,α-dichloroacetophenone, 29003-58-5; o-hydroxy-α,α-dichloroacetophenone bis(2,4-dinitrophenylosazone), 58463-01-7; 2,4-DNPH, 119-26-6.

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Nucleosides. 98. Direct Introduction of an Acetamido Group into the Sugar Moiety of Nucleoside Epoxides[1]

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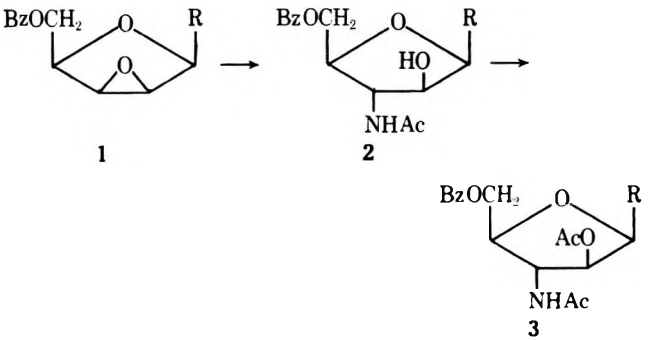
The interest in the synthesis of aminoglycosides (including amino nucleosides) has grown over the years owing to the antibiotic properties that many of them exhibit.[2] The most common method for the introduction of an amino group into a sugar is via nucleophilic displacement of a sulfonyloxy group by azide followed by reduction[3] or by opening an epoxide by ammonia.[4] In the case of nucleosides, an amino group may be introduced into the carbohydrate moiety by cyclization of nucleoside dialdehydes with nitromethane followed by reduction of the nitro group,[5] by replacement of a sulfonyloxy group,[6] or by opening an epoxide[7] or 2,2′-anhydro linkage[8] with azide and subsequent reduction of the azido function. Direct opening of nucleoside 2′,3′-epoxides with ammonia is also known.[9] We report herein a facile method for the *direct* introduction of an acylamino group into the sugar moiety of nucleosides by the use of boron trifluoride etherate in acetonitrile.

Treatment of the nucleoside 2′,3′-epoxides (**1**) with boron trifluoride etherate in acetonitrile followed by neutralization of the reaction mixture with saturated sodium hydrogen carbonate solution gave the corresponding 3′-acetamido-3′-deoxyarabinosyl nucleosides (**2**) which crystallized out in pure state from the reaction mixture (Chart I).

A plausible mechanism for the conversion of **1** → **2** via postulated intermediates **4** and **5** is shown (Chart II). This mechanism is somewhat akin to that proposed by Smith et al.[10] for the synthesis of oxazolines from epoxides. In the case of nucleoside 2′,3′-epoxides, however, anchimeric assistance from the 2′ oxygen in zwitterion **5** to form an oxazoline cannot occur. Hydrolysis of **5** results in the formation of 3′-acetamido-3′-deoxyarabinosyl nucleosides (**2**). It is noteworthy that TLC examination of the product **2** showed only one spot; no evidence for the formation of a 2′-acetamidoxylo nucleoside was obtained.

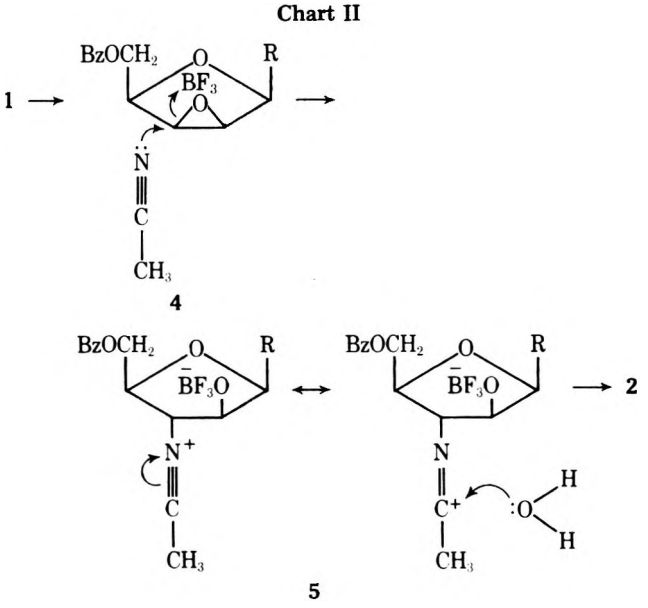
Chart I



1 2 3

a, R = uracil b, R = N^4-benzoylcytosine

Chart II



4 5 2

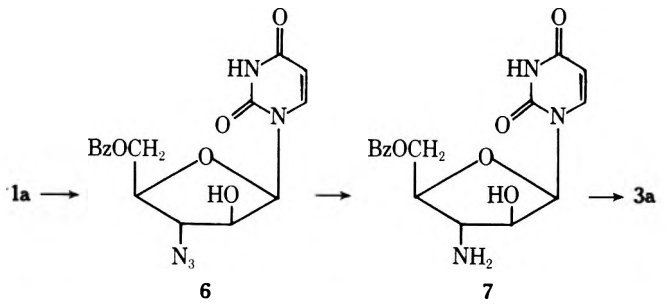
The structures of nucleosides **2** were established in the following manner: the position of the free hydroxyl group at C-2′ was confirmed by acylation of **2** to **3**, followed by NMR analyses of the acetylated products. In nucleosides **3** the sugar ring protons geminal to the acetoxy group are shifted downfield by ~1.2 ppm relative to their chemical shift in the parent compounds **2** (see NMR data in Experimental Section) and now appear as a triplet. Irradiation at the frequency of the triplet converted the doublet of the anomeric proton signal into a singlet. Upon irradiation at the frequency of the anomeric signal, the above mentioned triplet became a doublet. These decoupling experiments firmly allocate the hydroxyl substituent to C-2′ and, consequently, the acetamido function to C-3′ in **2** and **3**. Final proof was achieved by an unambiguous synthesis of 1-(3-acetamido-2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil and its identity with **3a** by NMR, ir, and mixture melting point. Thus, the lyxo epoxide **1a**[11] was treated with ammonium azide to afford **6** which was hydrogenolyzed to amino nucleoside **7** and acetylated to **3a** (Chart III).

Application of the boron trifluoride etherate–acetonitrile reagent combination to 2′,3′-epoxides of purine nucleosides is planned in our laboratory.

Experimental Section

NMR spectra were obtained on a JEOL J1M-PET-100 spectrometer with Me_4Si as reference. Chemical shifts are reported in parts per

Chart III



million (δ) and signals are described as s (singlet), d (doublet), t (triplet), and m (multiplet). Values given for coupling constants are first order. Ir spectra were recorded on a Perkin-Elmer Infracord using pressed KBr pellets. Melting points were determined on a Thomas-Hoover capillary apparatus. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-(2,3-Anhydro-β-D-lyxofuranosyl)cytosine. 2,2′-Anhydro-3′-*O*-mesylarabinofuranosylcytosine mesylate (2.0 g, 6 mmol)[12] was dissolved in water (20 ml) and potassium carbonate was added (1.0 g). After 2 h, more potassium carbonate was added (0.5 g) and the solution was allowed to stir at room temperature for 16 h. Excess Amberlite IRC-50 (H^+) was then added, and after stirring for 2 h the solution was filtered. The filtrate was concentrated and placed on a column of Dowex-50 (H^+). After washing thoroughly, the nucleoside was eluted with 1 N NH_4OH. Evaporation provided 0.9 g of an amorphous foam. TLC examination of the amorphous foam (90% ethanol) showed only two uv absorbing spots (R_f 0.46 and 0.20). Only the faster moving spot (major component) charred after sulfuric acid spray and also exhibited a positive test for epoxides with methyl red spray. This was used without further purification: NMR (Me_2SO-d_6) δ 3.59 (d, 2 H, H-5′, $J_{4',5'} \simeq 6$ Hz), 3.94–4.06 (two distorted doublets, 3 H, $J_{2',3'} \simeq 3$ Hz, superimposed on H-4′, J value not first order), 5.77 (d, 1 H, H-5, $J_{5,6} \simeq 8$ Hz), 6.08 (s, 1 H, H-1′), 7.57 (d, 1 H, H-6), 4.09 (broad s, 1 H, exchanged in D_2O), 7.20 (broad s, 2 H, exchanged in D_2O); uv λ_{max} (H_2O) 269 nm (neut), 277 nm (pH 1).

1-(2,3-Anhydro-5-*O*-benzoyl-β-D-lyxofuranosyl)-*N*⁴-benzoylcytosine (1b). The free epoxide (0.8 g) obtained above was treated with benzoic anhydride (2.5 g, 3 equiv) in dry pyridine (25 ml) for 12 h at room temperature and then for 3 h at 60 °C. The reaction mixture was poured into water (50 ml) and extracted with chloroform (50 ml × 3). The combined organic extracts were dried (sodium sulfate) and evaporated to dryness. The residue was crystallized from ethanol to afford **1b** as colorless needles, 0.62 g (40% based on crude epoxide), mp 187–190 °C.

Anal. Calcd for $C_{23}H_{19}N_3O_6$: C, 63.74; H, 4.38; N, 9.69. Found: C, 63.60; H. 4.29; N, 9.56.

1-(3-Acetamido-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (2a). To a suspension of the epoxide **1a**[11] (2.0 g, 6 mmol) in acetonitrile (25 ml, dried over P_2O_5) was added 4 ml of boron trifluoride etherate solution (5 equiv). A clear solution was obtained in a few minutes after the addition. The solution was stirred for 12 h at room temperature, then poured onto 40 ml of saturated sodium hydrogen carbonate solution. Compound **2a** precipitated out as colorless crystals which were filtered and washed with water and acetone, 1.5 g (64%), mp 230–234 °C (dec): NMR (Me_2SO-d_6) δ 1.87 (s, 3 H, NAc), 4.11 (m, 3 H, H-2′, H-3′, H-4′), 4.52 (d, 2 H, H-5′, $J_{4',5'} \simeq 4.3$ Hz), 5.49 (d, 1 H, H-5, $J_{5,6} \simeq 8.2$ Hz), 5.88 (d, 1 H, 2′-OH, $J_{2',OH} \simeq 4.6$ Hz), 6.10 (d, 1 H, H-1′, $J_{1',2'} \simeq 4.0$ Hz), 7.76 (m, 5 H, benzoyl), 8.40 (d, 1 H, H-6, $J_{5,6} \simeq 8.2$ Hz).

Anal. Calcd for $C_{18}H_{19}N_3O_7$: C, 55.52; H, 4.89; N, 10.76. Found: C, 55.42; H, 4.83; N, 10.63.

1-(3-Acetamido-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)-*N*⁴-benzoylcytosine (2b). By the same procedure as above, **2b** (1.95 g, 67.5%) was obtained as colorless crystals, mp 254–259 °C dec, from **1b** (2.6 g, 6 mmol): NMR (Me_2SO-d_6) δ 1.89 (s, 3 H, NAc), 4.20 (m, 3 H, H-2′, H-3′, H-4′), 4.56 (broad s, 2 H, H-5′), 5.89 (d, 1 H, 2′-OH, $J_{2'}$, OH ≃ 4.6 Hz), 6.21 (d, 1 H, H-1′, $J_{1',2'} \simeq 4.0$ Hz), 7.31 (d, 1 H, H-5, $J_{5,6} \simeq 7.3$ Hz), 7.81 (m, 10 H, benzoyl), 8.50 (d, 1 H, H-6, $J_{5,6} \simeq 7.3$ Hz).

Anal. Calcd for $C_{25}H_{24}N_4O_7$: C, 60.96; H, 4.87; N, 11.38. Found: C, 60.85; H, 4.92; N, 11.26.

1-(3-Acetamido-2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (3a). Compound **2a** (380 mg, 1 mmol) was dissolved in pyridine (15 ml) and 1 ml of acetic anhydride was added. The mixture was stirred for 2 h and then poured onto an ice–water mixture (25 ml). The mixture was extracted with chloroform (75 ml × 3) and the organic layer was dried (over sodium sulfate), evaporated to dryness, and then coevaporated several times with ethanol to remove traces of pyridine. The residue was crystallized from ethanol to give 360 mg of **3a** (85%) as colorless crystals, mp 208–210 °C: NMR (Me_2SO-d_6) δ 1.87 (s, 3 H, NAc), 1.89 (s, 3 H, OAc), 4.16 (m, 1 H, H-4′), 4.39 (m, 1 H, H-3′), 4.56 (d, 2 H, H-5′), 5.30 (t, 1 H, H-2′, $J_{1',2'} \simeq J_{2',3'} \simeq 5.5$ Hz), 5.55 (d, 1 H, H-5, $J_{5,6} \simeq 7.9$ Hz), 6.28 (d, 1 H, H-1′, $J_{1',2'} \simeq 5.5$ Hz), 7.79 (m, 5 H, benzoyl), 8.47 (d, 1 H, H-6, $J_{5,6} \simeq 7.9$ Hz).

Anal. Calcd for $C_{20}H_{21}N_3O_8$: C, 55.68; H, 4.87; N, 9.74. Found: C, 55.80; H, 4.96; N, 9.67.

1-(3-Acetamido-2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)-*N*⁴-benzoylcytosine (3b). Compound **2b** (100 mg, 0.25 mmol) was treated with acetic anhydride (1 ml) in pyridine (10 ml) for 2 h at room temperature and then poured onto water (20 ml). Colorless crystals precipitated, were collected and recrystallized from ethanol to give 86 mg of **3b** (80%), mp 136–141 °C: NMR (Me_2SO-d_6) δ 1.84 (s, 3 H, NAc), 1.89 (s, 3 H, OAc), 4.27 (m, 2 H, H-3′, H-4′), 4.60 (d, 2 H, H-5′), 5.45 (t, 1 H, H-2′, $J_{1',2'} \simeq J_{2',3'} \simeq 4.6$ Hz), 6.36 (d, 1 H, H-1′, $J_{1',2'} \simeq 4.6$ Hz), 7.35 (d, 1 H, H-5, $J_{5,6} \simeq 7.6$ Hz), 7.83 (m, 10 H, benzoyl), 8.58 (d, 1 H, H-6).

Anal. Calcd for $C_{27}H_{26}N_4O_8 \cdot H_2O$: C, 58.69; H, 5.07; N, 10.14. Found: C, 58.68; H, 4.96; N, 10.09.

The presence of H_2O was shown in NMR (Me_2SO-d_6) at δ 3.32.

1-(3-Azido-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (6). Compound **1a** (1.0 g) was added to ethanol (25 ml) containing ammonium azide (0.3 g). The mixture was refluxed for 22 h and the solution was evaporated. The residue was crystallized from 80% EtOH to give 1.1 g of **6** as colorless crystals, mp 150–153 °C. Recrystallization from methanol provided an analytical sample with mp 154–156 °C: NMR ($CDCl_3$) δ 4.20 (broad s, 2 H, H-5′), 4.6–4.8 (m, 3 H, H-2′, H-3′, H-4′), 5.31 (d, 1 H, H-5, $J_{5,6} \simeq 8$ Hz), 5.43 (broad s, 1 H, exchangeable, 2′-OH), 6.14 (d, 1 H, H-1′, $J_{1',2'} \simeq 3$ Hz), 7.40–7.84 (m, 4 H, benzoyl), 8.04–8.12 (distorted doublet, 2 H, H-6, $J_{5,6} \simeq 8$ Hz, and benzoyl).

Anal. Calcd for $C_{16}H_{15}N_5O_6$: C, 51.48; H, 4.05; N, 18.76. Found: C, 51.23; H, 4.19; N, 18.68.

1-(3-Acetamido-2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (3a). Compound **6** (159 mg) was dissolved in ethanol (15 ml) containing $CHCl_3$ (1 ml), and 10% Pd/C (90 mg) was added. The mixture was stirred at room temperature in a hydrogen atmosphere for 20 h and then filtered. The filtrate was decolorized with carbon and evaporated. The residue was dissolved in pyridine (5 ml) and acetic anhydride (1 ml) was added. After 5 h, methanol was added, and the solution was evaporated. The residue was crystallized from ethanol to yield **3a** (46 mg, mp 208–209 °C). The NMR, ir, and TLC behavior were identical with those for **3a** obtained as described above. The mixture melting point was undepressed.

Acknowledgment. The authors are indebted to Mr. Marvin Olsen for recording the NMR spectra.

Registry No.—**1a**, 14999-47-4; **1b**, 58540-92-4; **1b** free epoxide, 34989-27-0; **2a**, 58540-93-5; **2b**, 58540-94-6; **3a**, 58540-95-7; **3b**, 58540-96-8; **6**, 58540-97-9; 2,2′-anhydro-3′-*O*-mesylarabinofuranosylcytosine mesylate, 23463-73-2.

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Regiospecific 2,4-Diiodination of Resorcinol with Nascent Iodine

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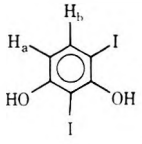
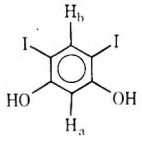
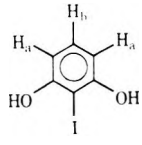
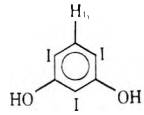
As part of a continuing effort to synthesize new x-ray contrast media, the iodination of hydroxyaryl precursors has achieved our attention. This note describes a new application of the $KIO_3/KI/HCl$ iodometric system[1] for iodination of the *m*-hydroxybenzenes, resorcinol and phloroglucinol.

A review of the literature dealing with the synthesis of mono-, di-, and trihalogenated resorcinols reveals the conspicuous absence of 2,4-diiodoresorcinol.[2,3] For example, diiodination of resorcinol with the interhalogen ICl (2 mol) in 20% aqueous HCl reportedly[4] provided the corresponding 4,6-diiodoresorcinol in 80% isolated yield. This experiment, repeated in our laboratory, gave crude 4,6-diiodoresorcinol which was isomerically pure as determined by NMR (Table I).

Table I. NMR Data (δ) for Iodinated Resorcinols

Compd	Structure	H_a	H_b
1		6.91,[a,b] d	7.63, d, J = 9 Hz, AB quartet
5		6.73, s	7.93, s
2		6.42,[b] d (unsym), 2 H J = 8 Hz	7.05, t (unsym), 1 H, J = 8 Hz
4		—	8.12, s

[a] NMR spectra (Me_2SO-d_6, D_2O, Me_4Si) were recorded on a Varian EM-360 spectrometer. D_2O was used to simplify the spectra by exchanging off the phenolic protons. [b] NMR data for these compounds also reported in ref 3.

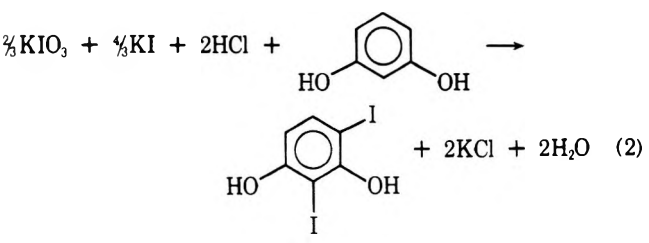
Moody and Thomas[5] detected the two-stage oxidation of iodide (eq 1) in aqueous HCl in the presence of iodate and

$$I^- \xrightarrow[HCl]{IO_3^-} \tfrac{1}{2}I_2 + e \xrightarrow[HCl]{IO_3^-} I^+ + e \qquad (1)$$

noted the "strong brown coloration" of the intermediate oxidation state, $\frac{1}{2}I_2$, i.e., nascent iodine. This work takes advantage of nascent iodine generated in situ as an iodinating species, (a) by using only stoichiometric amounts of all reagents, (b) by using reactive *m*-hydroxyaryls to rapidly react with the nascent iodine, and (c) by choosing the correct order of combination of reagents with substrate to preclude unwanted oxidations of both substrate and reagent.

Results and Discussion

Use of nascent iodine has resulted in the regiospecific 2,4-diiodination of resorcinol. In these experiments, stoichiometric amounts (eq 2) of aqueous KIO_3/KI were added



(2)

1

dropwise to aqueous resorcinol/HCl vigorously stirred at room temperature. Alternatively, aqueous KIO_3/HCl can be added dropwise to resorcinol/KI. With each drop of reagent a brown color developed immediately but dissipated in approximately 1 s, thereby iodinating resorcinol in a rapid reaction. NMR spectra taken on crude diiodination mixtures revealed only two products, 2,4-diiodoresorcinol (56%, isolated) and 2,4,6-triiodoresorcinol (Table II).

Table II. Iodination of Resorcinol with $KIO_3/KI/HCl$

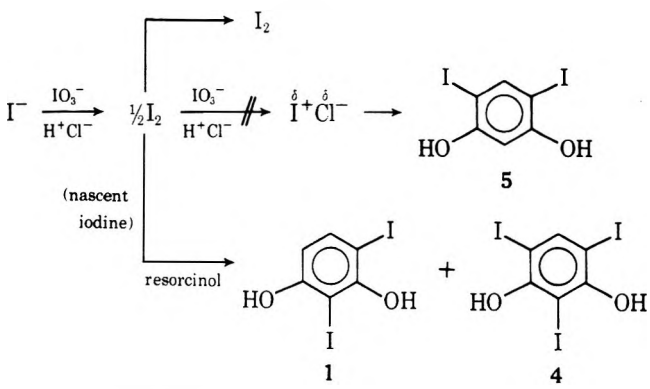
Stoichiometry[a] $KIO_3/KI/HCl$, mol	Product ratio[b,c] (1/4)	Yield, % (compd)
1/2/3	57/43	
$^2/_3/^4/_3/2$	89/11	56 (1)
$^1/_3/^2/_3/1$	*d*/0	32 (2)

[a] $IO_3^- + 5I^- + 6H^+ \rightarrow 3I_2 + 3H_2O$, see ref 1. The overall reaction stoichiometry is calculated for resorcinol iodination by I_2 and assuming HI as a product. [b] Crude product (EtOAc extracted) ratios determined by NMR integration of aromatic protons. [c] No evidence for 4,6-diiodoresorcinol observed in any crude products. [d] NMR of crude product mixture too complex to measure ratios and probably containing 4-iodo- and 2,4-diiodo- as well as 2-iodoresorcinol.

Monoiodination of resorcinol resulted in 2-iodoresorcinol (32%, isolated) but the crude mixture was too complex to determine products and ratios by NMR (Table II).

Triiodination of resorcinol gave primarily 2,4-diiodoresorcinol, the remainder being 2,4,6-triiodoresorcinol (Table II). This result suggests that for less reactive substrates such as diiodoresorcinol, dimerization (or deactivation) of nascent iodine to give molecular (or unreactive) iodine is a process in competition with iodination of the *m*-hydroxybenzene (Scheme I). However, the more reactive substrate phloroglucinol is triiodinated to 2,4,6-triiodophloroglucinol[6] (89%, isolated) in good yield.

Scheme I



By analogy to the action of ICl,[4] a source of "relatively positive" iodine, any I^+ (i.e., $I^{\delta+}Cl^{\delta-}$) formed in the redox reaction (eq 1, Scheme I) should have resulted in 4,6-diiodoresorcinol, but none was observed. Loss of nascent iodine to

give unreactive iodine results in decreased yields of iodination. It is anticipated that the KIO_3/KI/HCl system will complement the already used iodination methods opening the way to the synthesis of new iodoaryls.[7]

Experimental Section

General. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. Melting points are uncorrected and taken on a Thomas-Hoover apparatus. NMR spectra (Me_2SO-d_6, D_2O, Me_4Si) were recorded on a Varian EM 360. All evaporations were accomplished on a Buchi Rotovapor-RE at ≤45 °C. Resorcinol and phloroglucinol-$2H_2O$ were obtained from Aldrich Chemical Co., Milwaukee, Wis. ICl was obtained from Matheson Coleman and Bell.

2,4-Diiodoresorcinol (1). To 11.0 g (0.10 mol) of resorcinol in 250 ml of H_2O was added 16.7 ml (0.20 mol) of concentrated HCl. To this stirred solution was added at a drop rate over a 1-h period a second solution prepared from 14.3 g (0.067 mol) of KIO_3, 22.1 g (0.13 mol) of KI, and 500 ml of H_2O. (Note that nascent iodine color formed in situ after each drop dissipates in about 1 s.) Stirring was continued an additional 1.5 h before extracting the (essentially iodine free) reaction mixture with EtOAc (4 × 100 ml). Evaporation of the EtOAc layer gave an oil which was dissolved in boiling CCl_4, filtered while hot to clarify, then cooled to obtain 20.3 g (56%) of white solid title compound, mp 87–89 °C.[3]

Anal. Calcd for $C_6H_4I_2O_2$: C, 19.91; H, 1.11; I, 69.99. Found: C, 19.63; H, 1.02; I, 70.13.

2-Iodoresorcinol (2). Using the same procedure as for **1**, 11.0 g (0.10 mol) of resorcinol and 8.3 ml (0.10 mol) of concentrated HCl in 250 ml of H_2O was combined with 7.1 g (0.033 mol) of KIO_3 and 11.1 g (0.067 mol) of KI in 250 ml of H_2O. Thus was obtained an oil which was dissolved in $CHCl_3$ adjusted to turbidity with petroleum ether and placed in the freezer for several days to obtain tan solid. Twice recrystallized from benzene this material gave 7.6 g (32%) of white, crystalline **2**, mp 105–108 °C (lit.[2,3] 100 °C).

2,4,6-Triiodophloroglucinol (3).[6] To 10.0 g of phloroglucinol-$2H_2O$ (0.062 mol) slurried in 250 ml of H_2O with 15.1 ml (0.18 mol) of concentrated HCl was added at a drop rate, in 2 h, a solution of 13.2 g (0.062 mol) of KIO_3 and 20.5 g (0.12 mol) of KI in 400 ml of H_2O. The reaction slurry was stirred overnight and then the crude product collected by filtration, washed with H_2O, and dried in vacuo to obtain a pink powder, mp 160 °C dec. Recrystallization from boiling $CHCl_3$ gave 27.8 g (89%) of white, crystalline **3**, mp 171–172 °C dec. Anal. Calcd for $C_6H_3I_3O_3$: C, 14,30; H, 0.60; I, 75.57. Found: C, 14.56; H, 0.81; I, 75.51.

2,4,6-Triiodoresorcinol (4). A. Using the same procedure as for **1**, 5.5 g (0.050 mol) of resorcinol and 12.5 ml (0.15 mol) of concentrated HCl in 100 ml of H_2O was combined with 10.7 g (0.050 mol) of KIO_3 and 16.6 g (0.10 mol) of KI in 350 ml of H_2O. After stirring for an additional 2 h, Na_2SO_3 was added to decolorize (I_2) the reaction mixture, then EtOAc (4 × 100 ml) was used to extract all products. Evaporation of the organic layer gave tan solid dried in vacuo over P_2O_5 to give 19.3 g (79% of expected weight) of tan solid. NMR showed this material to consist of a 43/57 mixture of 2,4,6-triiodo- and 2,4-diiodorescorcinol, respectively.

B. Solid resorcinol (22.0 g, 0.20 mol) was added at once to a stirred solution of 875 ml of 0.8 N ICl in 1.6 N HCl and held at 50 °C for 1 h. Next Na_2SO_3 was added to decolorize (I_2) the mixture, and product was collected by filtration and recrystallized from boiling $CHCl_3$ to obtain 49.5 g (51%) of tan, crystalline **4**, mp 154–157 °C (lit.[2] 154 °C).

4,6-Diiodoresorcinol (5). Using the exact procedure of Nicolet and Sampey,[4] 5.0 g (30%) of crude white solid **5** was obtained, mp 145–158 °C (lit. 145 °C). NMR showed this compound to be isomerically pure (Table I).

Acknowledgments. This work was supported by the National Institutes of Health Grant GM 16593. My thanks also is deserved by Dr. Milos Sovak for his continuing encouragement and Mr. Terry Williams for his devoted assistance.

Registry No.—**1**, 41046-69-9; **2**, 41046-67-7; **3**, 57730-42-4; **4**, 19403-92-0; **5**, 19514-91-1; KIO_3, 7758-05-6; KI, 7681-11-0; resorcinol, 108-46-3; phloroglucinol, 108-73-6.

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(7) Attempted iodinations of catechol and hydroquinone using the same procedure as for resorcinol resulted in copious quantities of finely divided I_2. It was noted that the brown color of nascent iodine was not dissipated even after the first several drops; rather the reaction mixture became progressively darker and I_2 vapors progressively more apparent.

Stereochemistry and Conformation of Biogenetic Precursors of Indole Alkaloids[1]

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The biosynthetic pathway of indole alkaloids found in several plant genera, notably in the Apocynaceae family, commences with tryptophan and mevalonic acid.[3] Upon transformation of the latter into loganin (**1a**) and secologanin (**2a**) the metabolic substances meet in the form of vincoside (**3a**). It appears currently that **3a** or, in at least one instance, isovincoside (**3b**)[4] is a biogenetic precursor of many, structurally diverse indole alkaloids.[3,5] In order to facilitate investigations of the chemistry and metabolism of loganin (**1a**), secologanin (**2a**), the vincosides (**3a** and **3b**), and their lactams (**4a** and **4b**), provide NMR spectral parameters for the vincosides and the lactams, and reinforce and extend the ORD-based determination of the C(3) configuration of these substances,[6] a ^{13}C NMR analysis of **1a** and derivatives **1b**, **2b**, **3c–e**, and **4c,d** was undertaken.

The ^{13}C NMR analysis was initiated on the natural glucoside loganin (**1a**). The carbon shifts of the β-glucosyl unit were assigned on the basis of known literature values,[7] while all but the methine shifts were recognized by the characteristic field position and/or multiplicity of the signals of the unique aglycone carbon centers.[8] Carbon 19 was distinguished from the two other methines by its shift perturbation on acetylation of the neighboring 3-hydroxy group (vide infra). The differentiation of the remaining methines, C(15) and C(20), was founded on the shift difference of related carbons in dihydropyran and the expected strong deshielding of the homoallylic vs. allylic carbon by the neighboring methyl and glucosyloxy groups.

The ^{13}C NMR spectra of loganin pentaacetate (**1b**) revealed expected deshielding of C(3) and shielding of C(14) and C(19) as well as a shift pattern for the sugar moiety reminiscent of methyl tetraacetyl-β-D-glucopyranoside.[9] Rupturing the five-membered ring, i.e., loganin pentaacetate (**1b**) → secologanin tetraacetate (**2b**), caused no shift changes in the glucose unit, but induced ca. 2–5 ppm shift alterations for the characteristic dihydropyran ring carbons. The shift assignment for C(15) and C(20) of the secologanin derivative **2b** was confirmed by a correlation of the H(15) and H(20) shifts with the carbon resonances.[10,11] All δ values of compounds **1a**, **1b**, and **2b** are listed in Table I.

Table I. Carbon Shifts of Loganin and Secologanin Derivatives[a]

	1a[b]	1b[c]	2b[c]
C(3)	72.8	76.9	198.6
C(14)	40.9	38.7	43.0
C(15)	30.2	29.7	25.0
C(16)	112.0	113.3	109.2
C(17)	150.2	148.8	150.9
C(18)	11.4	12.3	120.7
C(19)	40.2	38.7	131.9
C(20)	44.6	45.3	43.5
C(21)	95.8	94.5	95.6
C=O	167.7	166.7	166.3
OMe	50.3	51.0	51.0
C(1′)	98.1	95.7	95.6
C(2′)	73.3	70.5	70.4
C(3′)	76.1	72.3[d]	72.2[d]
C(4′)	69.7	68.1	67.9
C(5′)	76.1	72.0[d]	72.0[d]
C(6′)	61.1	61.6	61.5

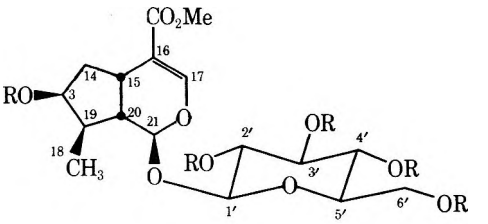
[a] δ values in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Enough methanol added to effect solution. [c] The acetyl groups show δ(Me) and δ(C=O) values of 20.4 ± 0.5 and 169.4 ± 0.9 ppm, respectively. [d] Signals may be reversed in any vertical column.

Table II. Carbon Shifts of Vincoside Derivatives[a]

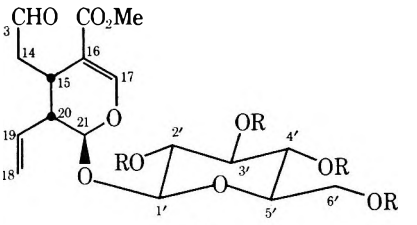
	3c[b]	3d[c]	3e[c]	4c	4d
C(2)	134.9	134.6	134.9	133.9	133.9
C(3)	51.1	45.9	47.7	53.3	53.6
C(5)	44.1	40.4	40.9	39.5	43.4
C(6)	16.9	21.5	21.5	21.1	19.0
C(7)	106.7	107.0	106.8	108.2	109.6
C(8)	127.2	126.6	126.4	126.9	127.7
C(9)	117.8	117.7	117.6	117.9	117.7
C(10)	118.9	119.1	119.0	119.0	119.0
C(11)	121.1	121.4	121.3	121.4	121.3
C(12)	110.6	110.9	111.0	111.2	111.4
C(13)	135.5	135.8	136.1	136.8	136.6
C(14)	33.7	33.1	33.4	31.5	26.3
C(15)	26.3	27.1	28.0	26.6	24.3
C(16)	111.7	110.9	110.3	109.1	109.6
C(17)	150.4	151.2	150.5	146.2	145.8
C(18)	119.4	120.1	120.9	119.8	119.9
C(19)	133.7	133.3	132.2	132.5	132.9
C(20)	42.1	42.8	43.4	42.7	42.9
C(21)	96.2	95.3	95.3	96.3	95.1
C=O	167.2	167.4	167.0	162.4	163.9
OMe	51.1	51.3	51.1		

[a] δ values in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. The tetraacetyl-β-D-glucopyranosyl carbon shifts are the same as those denoted in Table I. [b] The shifts for the benzyl group are $\delta(CH_2)$ 56.9, δ(ipso-C) 139.6, δ(o-C) 128.2, δ(m-C) 129.4, and δ(p-C) 126.7 ppm. [c] The carbonyl shift of the *N*-acetyl group is within the range of the δ values of the *O*-acetyl functions described in Table I, while the *N*-acetyl δ(Me) is 21.9 ppm.

The ^{13}C NMR data of secologanin tetraacetate (**2b**) (vide supra) and of tryptamine and carboline derivatives[12] permitted a first-order shift analysis of the tetraacetyl derivatives of N_b-benzylvincoside (**3c**), N_b-acetylvincoside (**3d**) and N_b-acetylisovincoside (**3e**). Inspection of the ^{13}C NMR spectra of vincoside lactam tetraacetate (**4c**) and the corresponding isovincoside derivative (**4d**) showed the ring closure of the vincosides to yield no ambiguous shift perturbations. All chemical shifts of compounds **3c–e** and **4c,d** are listed in Table II.

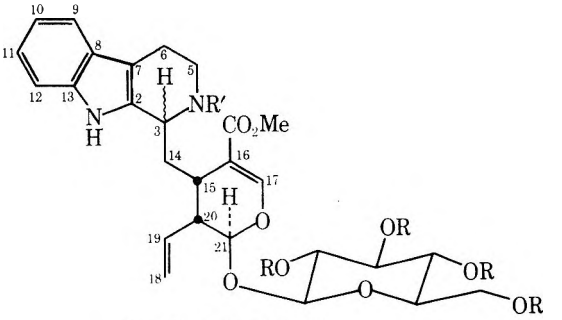


1

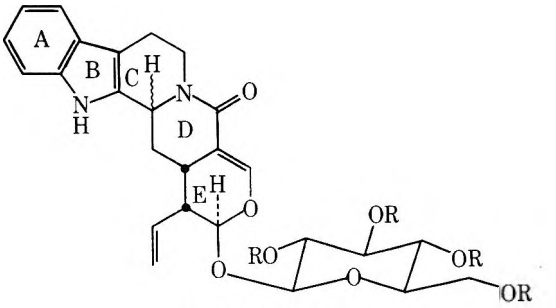


2

a, R = H
b, R = Ac



3a, 3β-H, R = R′ = H
b, 3α-H, R = R′ = H
c, 3β-H, R = Ac; R′ = $CH_2C_6H_5$
d, 3β-H, R = R′ = Ac
e, 3α-H, R = R′ = Ac

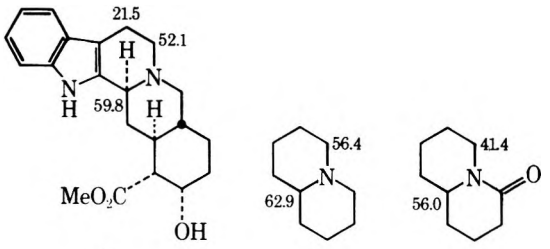


4a, 3β-H, R = H
b, 3α-H, R = H
c, 3β-H, R = Ac
d, 3α-H, R = Ac

Comparison of the ^{13}C NMR data on the N_b-acetylvincosides **3d** and **3e** shows C(3) epimerization to have little shift effect. The difference of the δ(C-3) values can be attributed to a difference of rotamer populations of the side chain whose exact nature is difficult to assess.[13] However, the shift difference of several carbon sites of tetraacetylvincoside lactam (**4c**) and tetraacetylisovincoside lactam (**4d**) reveals both the C(3) stereochemistry and the conformation of the fused pentacyclic nucleus of the two lactams.

The chemical shifts of C(3) and C(6) of yohimboid and ajmalicinoid alkaloids, pentacyclic substances (cf. **5**) structurally related to **4c** and **4d**, have been shown to be diagnostic parameters for the conformational analysis of these compounds.[14] Conversion of the quinolizidine unit,

i.e., rings C and D, into a quinolizidone system is expected to change the C(3) shift. Furthermore, the presence of a β-oxy-α,β-unsaturated carbonyl moiety flattens rings D and E to such an extent as to preclude nonbonded interactions between H(3) and ring E hydrogens or substituents, i.e., γ and δ effects. As a consequence the δ (C-3) value contains little stereochemical information, a prediction in accord with the identity of the C(3) shift of **4c** and **4d**. The Δδ value for the methine of quinolizidine (**6**)[12] and quinolizidone (**7**) can be used in conjunction with the C(3) shift of

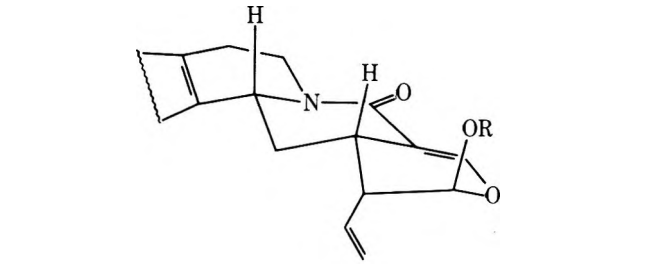


5 **6** **7**

yohimbine (**5**)[14] for the evaluation of δ (C-3) of **4c** and **4d**. The calculated value 52.9 ppm fits well the observed resonances of 53.3 and 53.6 ppm, respectively.

The δ (C-6) values of 21.5 ± 0.5 and 16.5 ± 0.5 ppm of yohimboid substances containing *trans*- and *cis*-quinolizidine units, respectively,[14] indicate **4c** to adopt the *trans*-quinolizidone conformation and **4d** to tend toward a *cis*-quinolizidone structure. While C(6) of **4d** is less shielded than expected, the limiting δ (C-6) value cannot be assessed. The lactam carbonyl group imposes trigonality on N_b thereby reducing nonbonded interactions on H(6) within a C/D cis conformation.[15] Finally, since **4c** and **4d** differ stereochemically only at C(3), the difference of their quinolizidone conformation limits them to H(3)–H(15) cis and trans stereochemistry, respectively.

Besides the C(6) shift three other resonances are in agreement with conformation 8 for lactam **4c** and **9a** for lactam **4d**. Comparison of the aminomethylene shift of quinolizidine (**6**) with the amidomethylene resonance of quinolizidone (**7**) yields a Δδ value of 15.0 ppm, while Δδ (C-5) between yohimbine (**5**) and tetraacetylvincoside lactam



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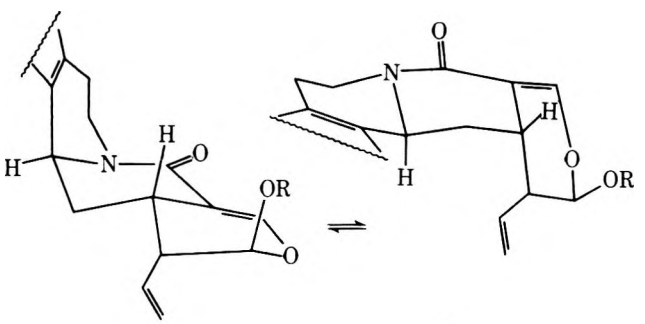

a **b**

9

(**4c**) as well as its 3 epimer **4d** is 12.6 and 8.7 ppm, respectively.[16] Since the shielding of C(5) on introduction of the nuclear carbonyl group is largely due to an added γ effect[17] and since the nonbonded interaction of the carbonyl oxygen with the C(5) hydrogens is nearly identical in the *trans*-quinolizidone conformations **8** and **9b** but different in the *cis*-quinolizidone form **9a**, the Δδ (C-5) values agree with the above conformational assignment. The γ effect of the carbonyl oxygen, which induces shielding of C(5) of **4c** relative to **4d**, is reflected also, albeit in reduced form, by the carbonyl carbon being more shielded in **4c** vs. **4d**. Carbon 19 experiences a 1,3-diaxial nonbonded interaction with H(14α) in conformations **8** and **9a**, but not in **9b**. Since the C(19) shift is nearly the same in **4c** and **4d**, it also confirms the above stereochemical argument.

Experimental Section

All carbon shifts were recorded on Brucker HFX-90E and Varian XL-100-15 NMR spectrometers operating in the Fourier transform mode at 22.6 and 25.2 MHz, respectively. The shifts on formulas **5**, **6**, and **7** refer to deuteriochloroform solutions; δ(Me_4Si) = δ($CDCl_3$) + 76.9 ppm.

Acknowledgment. A gift of lactams **4a** and **4b** by Dr. G. J. O'Loughlin, ^{13}C NMR determinations by J. Blackburn, and financial support by the Public Health Service for the work at the University of Wisconsin (CA 17127 by NCI) and at Rice University are acknowledged gratefully.

Registry No.—**1a**, 18524-94-2; **1b**, 20586-11-2; **2b**, 21237-36-5; **3c**, 55855-71-5; **3d**, 22621-93-8; **3e**, 20824-30-0; **4c**, 52484-98-7; **4d**, 23141-26-6.

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(16) If **4b** is compared with pseudoyohimbine,[14] a C/D cis structure, Δδ becomes 7.3 ppm.
(17) For sake of comparison the Δδ(Me) values of the methylcyclohexane/2-methylcyclohexanone and *N*-methylpiperidine/*N*-methyl-α-piperidone pairs are 9.5 and 12.1 ppm, respectively.

Catalysis of the Cope Rearrangement by Alumina

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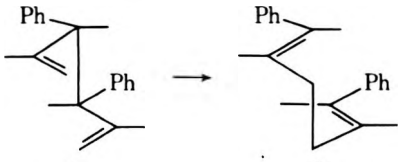
During attempted chromatographic purification of *dl*-3,4-diphenylhexa-1,5-diene (1) on alumina (Woelm 200, neutral, grade super I), the unexpected and surprising observation was made[1] that the diene had been partly converted to *trans,trans*-1,6-diphenylhexa-1,5-diene (2), the product of its thermal Cope rearrangement at 80 °C via a chairlike transition state (1a).[2] We report here a more detailed investigation of this phenomenon, including examination of the corresponding meso diene (3) which likewise rearranges on alumina, although at a considerably slower rate, to a product mixture comparable to that of its purely thermal Cope rearrangement, namely, *cis,trans*- (4) and *trans,trans*-1,6-diphenylhexa-1,5-diene (5).[2] To achieve convenient rearrangement rates, the commercial alumina was further activated for 4 h at 650–700 °C, a temperature which is reported to yield a catalyst of maximum activity.[3]



1a 2

With an alumina:diene ratio of 50:1, approximately 20 mg of *dl* diene (1) in 1 ml of heptane was converted within 15 min at room temperature to the trans,trans diene (2). The infrared spectrum of the crude product (84% material recovery) was virtually identical with that of authentic material, and VPC analysis showed less than 0.1% of other products under conditions where the three isomeric 1,6-diphenylhexa-1,5-dienes as well as *trans*-1,4-diphenylhexa-1,5-diene are resolved. Using Woelm 200 neutral alumina directly from its container without further activation, essentially equivalent results were obtained in 70 h at room temperature, as well as in 1.5 h at 60 °C. The uncatalyzed Cope rearrangement of the *dl* diene has a half-life of about 8 h at 80 °C and yields exclusively the trans,trans diene.[2]

Investigation of the meso diene rearrangement was complicated by incomplete conversions as well as alumina-catalyzed product isomerization. The extent of conversion could be determined by quantitative infrared spectroscopy on the crude rearrangement mixture, and product analysis was again carried out by VPC, after separation of the thermally labile unconverted meso diene by thin layer chromatography on silver nitrate impregnated silica gel.

Table I summarizes the results of two rearrangements at room temperature under conditions similar to those employed for *dl* diene. It is apparent from the leveling off of the percent rearrangement with time, especially in run 2, that the catalyst is becoming deactivated, and some product isomerization may be taking place. The inconsistencies in percent rearrangement with time are characteristic of the difficulties and poor reproducibility encountered in the investigation of the meso diene rearrangement. The sample points represent individual ampules, and the reaction is apparently sensitive to slight variations in the preparation and handling of the highly active catalyst. Accepting the data of run 1 as the more consistent, the alumina-catalyzed rearrangement of meso diene at room temperature gives 68% of *cis,trans*- (4) and 32% of *trans,trans*-1,6-diphenylhexa-1,5-diene (5).

Results of catalyzed rearrangement at 60 °C are given in Table II. Product isomerization is pronounced, and a rough approximation of the isomer ratio formed in the rearrangement itself, obtained by extrapolation to zero time, is 55% of cis,trans and 45% trans,trans isomers. Inconsistencies are again apparent in the extent of rearrangement vs. time.

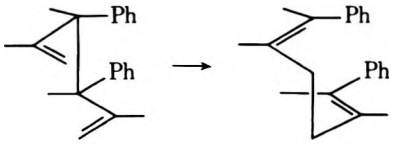
Table I. Meso Diene Rearrangement at Room Temperature

Run 1				
Reaction time, min	15	30	45	60
% meso diene rearranged	11	15	20	21
% cis,trans	68	68	68	68
% trans,trans	32	32	32	32
% material recovery	85	94	85	85
Run 2				
Reaction time, h	1	2	3	4
% meso diene rearranged	36	33	40	37
% cis,trans	73	72	68	69
% trans,trans	27	28	32	31
% material recovery	78	79	90	87

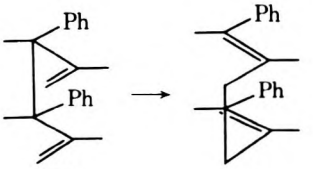
Table II. Meso Diene Rearrangement at 60 °C

Reaction time, min	15	30	45	60
% meso diene rearranged	53	96	82	"110"
% cis,trans	46	34	23	23
% trans,trans	54	66	77	77
% material recovery	95	75	90	73

The alumina-catalyzed rearrangement of the meso diene is likewise seen to parallel its purely thermal Cope rearrangement. In this case both the chairlike (**3a**) and boatlike (**3b**) configurations are involved, leading respectively to the cis,trans and trans,trans products. The thermal rearrangement gives 63% cis,trans and 37% trans,trans diene at 120 °C with a half-life of about 15 h.[2]



3a 4

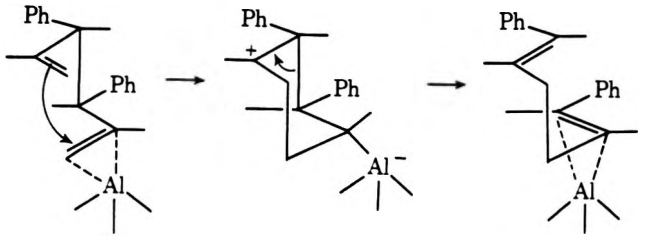


3b 5

To rule out the possibility that catalyzed rearrangement arises from a fragmentation–recombination process involving phenyl-substituted allyl radicals and *trans*-1,4-diphenylhexa-1,5-diene as intermediates, the latter was subjected to the conditions of catalyzed rearrangement. It was unaffected by this treatment, and was also not detected in any of the crude rearrangement products.

The parallelism between the alumina-catalyzed and thermal reactions suggests that catalysis involves interaction of only one double bond with the catalyst surface, leaving the other free to adopt the preferred configuration. Assuming that catalysis by alumina is a consequence of Lewis acidity, some variation of the process illustrated in Scheme I for the *dl* diene may be operating in the catalyzed reaction.

Scheme I



A few examples of catalyzed Cope rearrangements have been previously reported, each involving a transition metal complex.[4] The oxa-Cope (Claisen) rearrangement is catalyzed by more or less ordinary Lewis acids.[5]

Experimental Section

Melting points are uncorrected and were obtained in capillary tubes. Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrophotometer. VPC analysis of the systems under study has already been described.[2] TLC analyses were on silica gel (Merck, HF_{254}) impregnated with about 20% silver nitrate, with sample components directly visible under short-wavelength uv light or upon spraying with 2,7-dichlorofluorescein followed by long-wavelength uv. Except where noted, alumina (Woelm 200, neutral, grade super I, approximately 200 m^2/g BET surface area) was activated at 650–700 °C for 4 h prior to use. Weighings of alumina were carried out in a drybox. *n*-Heptane (Mallinckrodt spectrophotometric grade) was dried over molecular sieves.

Rearrangement of *dl*-3,4-Diphenylhexa-1,5-diene on Aluminum Oxide. Approximately 1 g of alumina was weighed into each of four 5-ml Pyrex ampules; into each ampule was injected a solution of *dl* diene (mp 34.7–35.6 °C) in *n*-heptane (20 mg/ml) in such quantity that the diene:alumina ratio was 1:50. The ampules were closed with serum caps and left at room temperature with frequent manual shaking for 15, 30, 45, and 60 min, respectively. Crude products were isolated by vacuum evaporation of solvent after filtration and rinsing of the pale yellow alumina with a small amount of methanol. The ir spectra of all samples were virtually identical with that of authentic *trans,trans*-1,6-diphenylhexa-1,5-diene. VPC confirmed that this was the major component, with only traces of other materials; isomeric 1,6-diphenylhexa-1,5-dienes were absent in amounts greater than 0.1%. Melting points and percent material recovery for the crude samples follow: 15 min (84%), mp 74.0–77.2 °C; 30 min (94%), 73.5–76.7 °C; 45 min (87%), 75.5–77.5 °C; 60 min (84%), 73.5–76.0 °C; lit.[2] 79.0–79.5 °C.

Another run used 20 mg of *dl* diene in 2 ml of *n*-heptane with 2 g of Woelm alumina taken directly from its container without further heating. Rearrangement was monitored by TLC (development in 1:1 carbon tetrachloride–acetone); the reaction appeared complete after 70 h. The crude product, mp 73.5–76.0 °C, analyzed by VPC as *trans,trans*-1,6-diphenylhexa-1,5-diene with only traces of other components.

A similar run was carried out at 60 °C with 40 mg of *dl* diene in 2 ml of *n*-heptane and 2 g of Woelm alumina taken directly from its container. VPC analysis of the crude product (mp 76.0–77.5 °C) after 1.5 h showed no significant components other than the trans,trans diene.

Rearrangement of *meso*-3,4-Diphenylhexa-1,5-diene on Aluminum Oxide. Run 1. Into each of four ampules containing approximately 1 g of alumina was injected a solution of meso diene (mp 85.6–86.5 °C) in *n*-heptane (25 mg/ml) in such quantity that the diene:alumina ratio was 1:50. Crude products were isolated after 15, 30, 45, and 60 min at room temperature. The ir spectrum of each was determined quantitatively, following which unreacted meso diene was removed by preparative TLC (70:30 carbon tetrachloride–acetone). The faster moving unresolved 1,6-diphenylhexa-1,5-dienes were eluted from the silica gel with dichloromethane. VPC analysis identified *cis,trans*- and *trans,trans*-1,6-diphenylhexa-1,5-diene as the only products present in other than trace amount, with their relative ratios determined by integration. The percent conversion for each sample was determined from the intensity of the 10.4-μ ir band common to the two dienes, employing an average extinction coefficient calculated from the VPC data and the extinction coefficients for the pure cis,trans diene (0.67 ml mg^{-1} cm^{-1}) and the trans,trans diene (1.97 ml mg^{-1} cm^{-1}). Results are shown in Table I.

Run 2. In a second run ampules were kept at room temperature for 1, 2, 3, and 4 h, respectively. Results are given in Table I. Characteristics of this run were similar to those of the earlier one, except that the later samples showed a slight unidentified shoulder on the downward slope of the VPC trace of the trans,trans diene.

A third run was carried out at 60 °C, with crude products isolated at 15, 30, 45, and 60 min. Results are given in Table II. A trace component with a retention time corresponding to that of *cis,cis*-1,6-diphenylhexa-1,5-diene could also be observed in the VPC traces. The "110%" conversion in 60 min probably reflects inability to isolate product absorption at 10.4 μ from background ir absorption, since pure trans,trans diene showed linearity in the concentration range employed. Visual inspection of the ir spectrum actually suggested approximately 5% unreacted meso diene after 60 min. No attempt was made to improve the ir analysis in view of the inherent lack of reproducibility encountered and expected in a heterogeneous system involving a highly activated alumina.

Stability of *trans*-1,4-Diphenylhexa-1,5-diene on Alumina. Two ampules prepared as above using *trans*-1,4-diphenylhexa-1,5-diene in *n*-heptane were maintained, respectively, at room temperature for 4 h and at 60 °C for 1 h. Isolation of the diene followed by ir and VPC examination showed that the trans 1,4-diene had undergone no change.

Registry No.—1, 33788-15-7; 2, 58463-02-8; 3, 33788-14-6; 4, 33788-20-4; alumina, 1344-28-1.

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Carboxylation of Aromatic Compounds by Palladium(II) Carboxylates

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Benzenoid compounds react with palladium(II) salts in a variety of ways, depending on the reaction conditions used. The products resulting from chlorination,[1] acetoxylation,[2] nitration,[3] carbonylation,[4] and oxidative dimerization[5] are known. The authors have already communicated a newer type of reaction by palladium(II) chloride and sodium acetate, i.e., aromatic carboxylation.[6] However, the yields of aromatic acids therein produced were relatively poor.

The present paper describes that the use of palladium(II) carboxylates improves the yields of aromatic acids and that the olefinic hydrogen of styrene is also substituted by carboxyl group, although in a low yield.

The reaction of aromatic compounds with sodium palladium(II) malonate (A)[7] in a mixed solvent of acetic acids and acetic anhydride or carbon tetrachloride gave aromatic acids in good yields, together with lower yields of aromatic dimers. The results are shown in Table I. It can be seen that sodium palladium(II) malonate (A) is much more efficient for aromatic carboxylation than the palladium(II) chloride–sodium acetate system.[6]

Table I. Carboxylation of Aromatic Compounds by Sodium Palladium(II) Malonate (A)

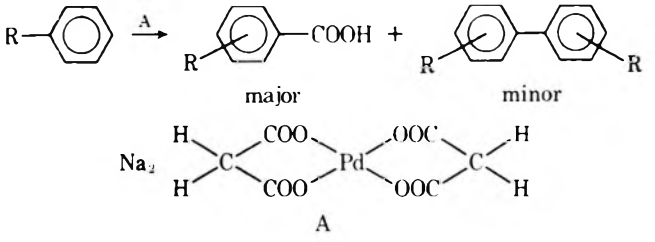
Reactants[a]			Products, %[b]	
R—⬡ (0.1 mol)	A, mmol	Solvents (ratio) (100 ml)	R—⬡—COOH	R—⬡—⬡—R
R = H	1.4	AcOH–Ac_2O (1:1)	98	None
H	2.8	AcOH–Ac_2O (1:1)	70	Trace
H	2.8	AcOH–CCl_4 (5:1)	66	20
OCH_3	2.8	AcOH–CCl_4 (5:1)	55.4	Small

[a] Reactants were heated at 100 °C or reflux for 10 h. [b] Yields are based on A used.

Table II. Carboxylation of Aromatic Compounds by Palladium(II) Malonate Complex (A) in the Presence of Silver Acetate

Registry no.	Reactants[a] aromatic compd (mmol)	Products (%)[b] Aromatic acids	Aromatic dimers
71-43-2	⬡ (113)	⬡—COOH (72)	⬡—⬡ (20)
100-66-3	⬡—OCH_3 (92)	CH_3O—⬡—COOH (111)[c]	CH_3O—⬡—⬡—OCH_3 (20)
108-88-3	⬡—CH_3 (94)	CH_3—⬡—COOH (51)[c]	ND[d]
93-58-3	⬡—$COOCH_3$ (81)	H_3COOC—⬡—COOH (30)[e]	H_3COOC—⬡—⬡—$COOCH_3$ (5)
91-20-3	⬡⬡ (90)	⬡⬡—COOH (90)[f]	⬡⬡—⬡⬡ (15)
110-00-9	⬠ (138)	⬠—COOH (101)[c]	ND[d]

[a] The complex A (2.8 mmol), AgOAc (12 mmol), and aromatic compound (10 ml) were allowed to react in the mixed solvent (96 ml) of acetic acid and carbon tetrachloride (5:1). [b] Yields are based on the complex A used. [c] Exclusively formed. [d] Not determined. [e] The meta isomer (80%) and para isomer (20%) were formed. [f] The formation ratio of α and β isomer was 2:1.



A

When silver acetate was used in addition to the salt (A), the best yield of aromatic acid was raised to 111%, based on palladium(II) salt used. The results for various aromatic compounds are summarized in Table II. The addition of reoxidation agent for metallic palladium(0) may make palladium-catalyzed carboxylation possible. Even though reoxidation of palladium(0) during the present reaction may produce palladium(II) acetate rather than regenerate sodium palladium(II) malonate (A), it is emphasized that the catalytic reaction is possible, as palladium(II) acetate also introduces the carboxyl group into aromatic rings. The attempted reactions of palladium(II) acetate with benzene under similar conditions gave benzoic acid in yields of 18–21%.

The difference in yields between A and palladium(II) acetate suggests that carboxylate ions around the palladium atom have an important role upon the aromatic carboxylation.[8] Furthermore, the carboxylation of benzene by palladium(II) acetate occurred in other solvents, such as acetic anhydride (in a yield of 21%), isobutyric anhydride (64%), or tetrachloroethylene (10%), showing that the carbon atom introduced into the aromatic ring should not be derived from solvent molecules. Further supporting evidence for this inference may be the result of reactions of phenylmercury compounds with palladium(II) salts in the mixed solvent of acetic acid and acetic anhydride (Table III). The substitution of mercury atom with carboxyl group was successful only in the presence of acetate ion. Consequently, these observations elucidate that the carbon atom of the carboxyl group introduced should be derived from carboxylate ions (e.g., malonate or acetate ions) which may be bonded to palladium atom.

The reaction of styrene with palladium(II) salt was further investigated, in order to know the scope of the carboxylation. The result showed that the olefinic hydrogen of styrene was

Table III. Reaction of Phenylmercury Compounds with Palladium(II) Salts

Reactants[a]			Products, %[b]			
Pd Salt (5 mmol)	PhHg salt (5 mmol)	Na salt (50 mmol)	⬡—COOH	⬡—⬡	⬡—OAc	⬡—Cl
$PdCl_2$	PhHgCl	NaCl	Trace	45	None	52
$PdCl_2$	PhHgCl	NaOAc	11	48	Trace	ND[c]
$Pd(OAc)_2$	PhHgOAc	NaOAc	60	1.0	2.0	

[a] Reactants were heated in the mixed solvent of acetic acid (100 ml) and acetic anhydride (50 ml) at 100 °C for 5 hr. [b] Yields are based on phenylmercury compounds used. [c] Not determined

substituted by carboxyl group to give olefinic acid, although in a low yield. In a typical experiment, styrene was allowed to react with palladium(II) chloride and sodium acetate in a mixed solvent of acetic acid and acetic anhydride, to give cinnamic acid (trace) and 3-phenylallylic acid (2.6%), together with 1,4-diphenylbutadiene (2.4%) and β-acetoxystyrene (23.3%). Furthermore, the reaction of styrene with palladium(II) chloride and sodium propionate in a mixed solvent of propionic acid and propionic anhydride gave cinnamic acid (5.0%), in addition to 1,4-diphenylbutadiene (9.0%) and β-propioxystyrene (44.0%).

Experimental Section

Materials. Commercially available palladium(II) chloride (a guaranteed reagent by Tokyo Kasei Kogyo Co. Ltd.) was powdered and used without further purification. Palladium(II) acetate was prepared according to the method of Stephenson et al.[9] Thiophene-free benzenes were used after drying by Na wire. Sodium acetate was dried by heating in solid state before use. Malonic acid and the sodium salt were commercially available. All solvents were distilled and dried by sodium sulfate. All authentic aromatic acids and dimers were commercially available and compared with isolated products in melting point, ir, NMR, and GLC retention time.

Sodium Palladium(II) Malonate (A). A mixture of palladium(II) chloride (3.6 g, 0.02 mol) and sodium malonate (6.0 g, 0.04 mol) in water (60 ml) was stirred on a boiling water bath. The brown mixture was gradually changed to a yellow precipitate. After 1 h, the yellow precipitate was filtered out (60% yield). The addition of acetone to the concentrated mother liquid gave further precipitate. The collected solids were recrystallized from water: yellow needles, mp 198–200 °C dec; ir data was identical with that of potassium palladium(II) malonate, prepared by Schmerz et al.[10]

Anal. Calcd for $C_6H_4O_8Na_2Pd$: C, 20.20; H, 1.12. Found: C, 20.31; H, 1.04.

A was also synthesized from the reaction in nonaqueous system. Namely, the reaction of palladium(II) chloride and sodium malonate (1:2) in a mixed solvent of acetic acid and carbon tetrachloride (1:1) under reflux for 5 h gave a yellow palladium(II) compound in a yield of 90%. The isolated compound was identical with A from the preceding reaction in all spectral data.

Carboxylation of Benzene by Palladium(II) Acetate. A stirred solution of palladium(II) acetate (4.5 g, 0.02 mol), sodium acetate (8.2 g, 0.1 mol), and benzene (15.6 g, 0.2 mol) in a mixed solvent of acetic acid (100 ml) and acetic anhydride (100 ml) was heated at 100 °C for 6 h under nitrogen. The initial clear brown solution gradually turned black, showing precipitation of metallic palladium. After 6 h, gas evolution almost ceased, whose total amount was 71 ml and consisted of carbon dioxide, confirmed by GLC analysis, using a 3-m, 20% acetonylacetone on Neopac 1A column (0 °C, He carrier). Metallic palladium (2.1 g, 95%) was removed by filtration. Distillation of the filtrate gave a low-boiling fraction I (40–80 °C) and a high-boiling fraction II (80–136 °C). Fraction I contained methyl acetate, benzene, and acetic acid, by GLC analysis using a 1.5-m, silicon DC 550 on Celite 545 column (50 °C, H_2 carrier) and a 1.5-m, polyethylene glycol 20M on Celite 545 column (30 °C, H_2 carrier). Redistillation of fraction I gave a small amount of almost pure methyl acetate, which was identical with authentic material in ir spectrum. Fraction II consisted of benzene, acetic acid, and acetic anhydride. Further distillation of the residue under a reduced pressure removed residual solvents. The residual mixture was basified by aqueous sodium carbonate (15%) and extracted several times by diethyl ether. Then the aqueous layer was acidified by concentrated hydrogen chloride and similarly extracted. The ether extracts were dried over anhydrous sodium sulfate. The acidic ether extract gave 526 mg of benzoic acid (21%): needles from water, mp 121–122 °C (lit. mp 122°C). The neutral ether extract gave 118 mg of acetophenone (5%), 44 mg of phenyl acetate (1.5%), and a trace of biphenyl, which were identified with authentic materials by GLC and ir.

The reactions under other conditions were similarly treated. However, other products, except benzoic acid and biphenyl, were not identified.

Carboxylation of Benzene by A. A mixture of aromatic compounds (0.1 mol) and A (1.4 or 2.8 mmol) was heated under nitrogen for 19 h at 100 °C in a mixed solvent (100 ml) of acetic acid and acetic anhydride (1:1) or under reflux in a mixed solvent (100 ml) of acetic acid and carbon tetrachloride (5:1). The reaction mixtures were similarly treated as described in the above reaction.

Carboxylation of Aromatic Compounds by A in the Presence of Silver Acetate. A mixture of aromatic compounds (ca. 10 ml),[11] A (1.0 g, 2.8 mmol), and silver acetate (3.0 g, 12 mmol) was heated in a mixed solvent of acetic acid (80 ml) and carbon tetrachloride (16 ml) under reflux for 10 h. The reaction mixtures were similarly treated as described above. The isolated aromatic products were identified with the authentic materials by ir, NMR, and mass spectra. The isomer distribution of aromatic acids was determined by GLC analysis, after the esterification with diazomethane.

Reaction of Phenylmercury Compounds with Palladium(II) Salts. Palladium(II) acetate (1.1 g, 5 mmol) was allowed to react with phenylmercuric acetate (1.7 g, 5 mmol) in the presence of sodium acetate (4.1 g, 50 mmol) in a mixed solvent of acetic acid (100 ml) and acetic anhydride (50 ml) at 100 °C for 5 h. The reaction mixture was treated as described above. An acidic part (367 mg) of products contained benzoic acid (350 mg, 3 mmol). Biphenyl and phenyl acetate were identified by GLC analysis of the neutral part (70 mg).

Competitive Carboxylation of Benzene and Hexadeuteriobenzene by Palladium(II) Acetate. A mixture of benzene (49.4 mmol) and hexadeuteriobenzene (44.5 mmol) was carboxylated by palladium(II) acetate (2.2 g, 0.01 mol) and sodium acetate (8.2 g, 0.1 mol) in a mixed solvent of acetic acid (50 ml) and acetic anhydride (50 ml) at 100 °C for 5 h. After the filtration of precipitated metallic palladium and then evaporation of solvents and unreacted benzenes, the residual mixture was basified by aqueous sodium carbonate and washed several times by ethyl ether. Then the aqueous solution was acidified by concentrated hydrochloric acid and extracted by 100 ml of ethyl ether. The ether extract was dried over anhydrous sodium sulfate. After evaporation of ether, the residual mixture of aromatic acids (277 mg) was analyzed by mass spectra, which showed two peaks at the mass number of 127 and 122 with relative peak height of 1.00 and 4.38, respectively.

Competitive Carboxylation of Benzene and Hexadeuteriobenzene by A. A mixture of benzene (4.23 g, 54.2 mmol) and hexadeuteriobenzene (4.57 g, 54.4 mmol) was allowed to react with A (1.0 g, 6.8 mmol) in a mixed solvent of acetic acid (80 ml) and carbon tetrachloride (16 ml) under reflux (92 °C) for 5 h. After the treatment described in the reaction with palladium(II) acetate, both the acidic products (58.5 mg) and the neutral products (small amount) were analyzed by mass spectra. The acidic part had two peaks at the mass number of 127 and 122 with relative peak height of 1.00 and 3.90, respectively, corresponding to pentadeuteriobenzoic acid and benzoic acid. The neutral part had three peaks at the mass number 164, 159, and 154 with relative intensity of 1.00, 6.08, and 12.9, respectively, corresponding to decadeuteriodiphenyl, pentadeuteriodiphenyl, and diphenyl. Thus the relative number of phenyl group and pentadeuteriophenyl group in the produced aromatic dimers was 3.9 and 1.0, respectively.

Reaction of Styrene with Palladium(II) Chloride and Sodium Acetate. A stirred mixture of styrene (52.1 g, 0.5 mol), palladium(II) chloride (7.2 g, 0.04 mol), and sodium acetate (16.4 g, 0.2 mol) was heated in a mixed solvent of acetic acid (600 ml) and acetic anhydride (300 ml) at 105 °C for 7 h under nitrogen. The acidic products and the neutral products were separated by a similar treatment of the reaction mixture as described in the reaction of palladium(II) acetate. The distillation of the acidic part under a reduced pressure (1–2 mmHg) gave white sublimate (5 mg): mp 131–132 °C (lit. mp 133 °C); the ir identical with that of a specimen of cinnamic acid. The distillation residue (630 mg) was dissolved into water. Water-soluble substances were recovered and recrystallized from water. 3-Phenylallylic acid (167 mg) was isolated and further purified by sublimation: mp 85–86 °C; ir (KBr disk) 2750–2450, 1700, 1410, 1222 (-COOH), 3040, 748, 695 (-Ph), 972 cm^{-1} (trans HC=CH); NMR (CCl_4) τ 6.80 (d, 2 H), 2.85–4.10 (m, 2 H), 2.79 (s, 5 H), −1.76 (s, 1 H).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.07; H, 6.17. Found: C, 74.10; H, 6.19.

The neutral part was filtered after evaporation of ethyl ether and cooling of the oily liquid to give 1,4-diphenylbutadiene (200 mg): pale yellow leaflets from benzene, mp 152–153 °C (lit. mp 153 °C); NMR (CCl_4) τ 2.65–3.70 (m); ir (KBr disk) 3060, 1603, 1580, 1500, 1450, 1073, 992, 988, 912, 745, 736, 687 cm^{-1}. The filtrate was distilled under a reduced pressure (2 mmHg) to collect a fraction I (30–93 °C, 2 mmHg). Redistillation of fraction I gave 1.5 g of β-acetoxystyrene: bp 88–91 °C (2 mmHg); $n^{18}D$ 1.5491 [lit.[12] bp 119–121 °C (10 mmHg), $n^{24}D$ 1.5483]; ir 1758, 1220, 1103 (-OAc), 3060, 1655, 940 (-HC=CH-), 1600, 758, 700 cm^{-1} (-Ph); NMR (CCl_4) τ 2.25 (d, 1 H), 2.82 (s, 5 H), 3.74 (d, 1 H), 7.9 (s, 3 H). The residual oily liquid is considered to contain saturated acetate compounds and oligomers of styrene from the spectral data.

Reaction of Styrene with Palladium(II) Chloride and Sodium Acetate. A stirred mixture of styrene (52.1 g, 0.5 mol), palladium(II) chloride (3.6 g, 0.02 mol), and sodium propionate (9.6 g, 0.1 mol) was

heated in a mixed solvent of propionic acid (98.4 g) and propionic anhydride (91.0 g) at 103 °C for 7.5 h under nitrogen. After the treatment described above, cinnamic acid (324 mg, 5.0%), 1,4-diphenylbutadiene (380 mg, 9.0%), and β-propioxystyrene (1.5 g, 44%) were isolated.

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Registry No.—A, 31168-61-3; palladium(II) chloride, 7647-10-1; sodium malonate, 23549-97-5; palladium(II) acetate, 3375-31-3; styrene, 100-42-5; sodium acetate, 127-09-3; phenylallylic acid, 2243-53-0; 1,4-diphenylbutadiene, 886-65-7; β-acetoxystyrene, 10521-96-7; PhHgCl, 100-56-1; PhHgOAc, 62-38-4.

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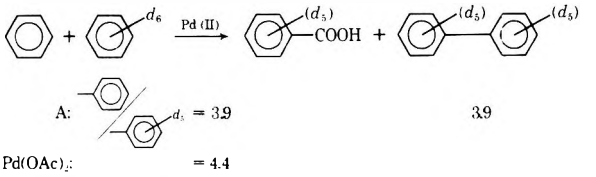

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Synthesis of 4-Lithio-2-methyl-2-pentene. A New Type of Allylic Organometallic Compound[1]

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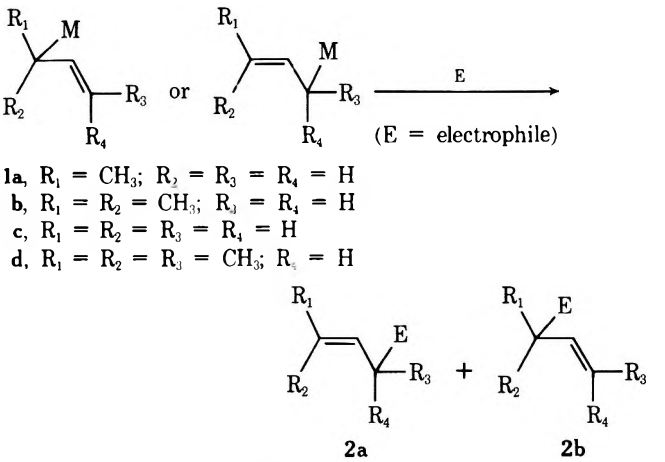
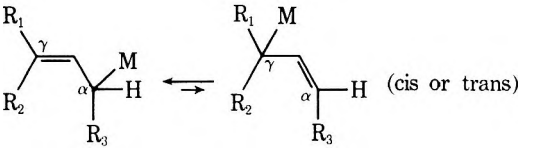
Allylic organometallics have long been the subject of intensive investigation.[2] In particular, the ability of unsymmetrical allylic organometallics (1) to attach themselves to electrophiles by either end of the allylic system (**2a** and **2b**) (Scheme I) has interested many workers. The nature of some electrophiles (alkyl halide, mineral acid, carbon dioxide) can greatly affect the ratio of these two possible product types.[3] It is, therefore, difficult to say anything about the point of attachment of the metal in the organometallic species unless some physical method such as NMR is used as a probe.

Fortunately, much NMR work has been done and compounds such as 2-butenyl (crotyl)[4] (**1a**), 2-methyl-2-butenyl[5] (**1b**), and propenyl (allyl)[6] (**1c**) Grignard reagents have been investigated. In each of the above cases where the allylic system is unsymmetrical (**1a** and **1b**), the organometallic compound has been shown to be a rapidly interconverting mixture of isomeric compounds (Scheme II). The predominant isomer

Scheme I



Scheme II



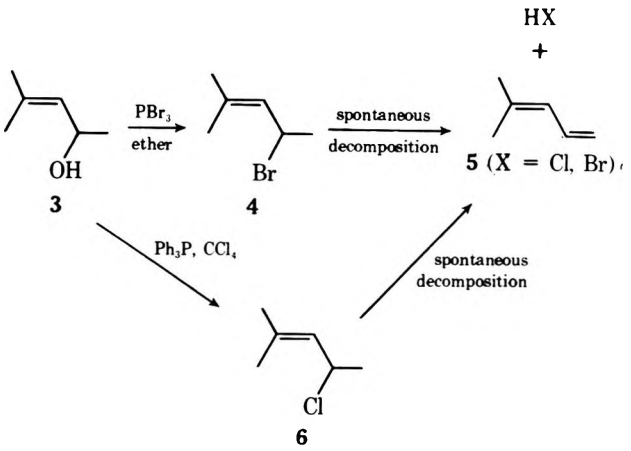
is always the isomer in which the metal is attached to the *least* substituted end of the allylic system (herein termed the α carbon).[4,5] The isomer with metal attached to the most substituted carbon (herein termed the γ carbon) is presumably present in only small quantities at room temperature.[5]

To date, all investigation concerning unsymmetrical allylic organometallics where all the nonhydrogen substituents on the α and γ carbons are alkyl has been with systems where the point of metal attachment may be either on a primary or secondary allylic carbon (crotyl and related systems) or a primary or tertiary allylic carbon (2-methyl-2-butenyl and related systems). No simple allylic organometallic in which the position of attachment of the metal atom may be on either a secondary and tertiary allylic carbon has been synthesized and studied. We now wish to report the synthesis of such a system, namely 4-lithio-2-methyl-2-pentene (**1d**), and the results of several reactions of this new organometallic with several carbonyl compounds.

Generally, the synthesis of allylic organometallics can easily be effected from the corresponding bromide or chloride. With this in mind, we attempted to synthesize 4-bromo-2-methyl-2-pentene (**4**) from 2-methyl-2-penten-4-ol (**3**) using phosphorus tribromide in ether (Scheme III), a method reported by Roberts and co-workers for the synthesis of **4**.[7a] The results of this attempt were disappointing as the bromide spontaneously decomposed to give HBr and what NMR studies indicated to be 4,4-dimethyl-1,3-butadiene (**5**). The report by Roberts is, it should be noted, the only reference in the chemical literature to the synthesis of **4**.[7b] Similar results were obtained when the synthesis of 4-chloro-2-methyl-2-pentene (**6**) was attempted using **3** and a mixture of triphenylphosphine and carbon tetrachloride, a method reported to be suitable for the synthesis of allylic chlorides which are prone to rearrangement.[8] Presumably, the extreme difficulty of obtaining these halides in pure form under normal conditions accounts for the fact that the corresponding allylic anion (**1d**) and related systems have not been prepared.

Mesitoate esters of allylic alcohols, however, have been

Scheme III



shown to be good in situ sources of allylic anions when treated with lithium metal in tetrahydrofuran in the presence of allylic halides, aldehydes, or ketones.[9] The mesitoate ester of **3**, 4-(2-methyl-2-pentenyl) mesitoate (**7**), was therefore prepared by treating that alcohol with mesitoyl chloride in chloroform.[9] Since reaction of the resulting in situ generated allyllithium with electrophile is extremely rapid, this method of synthesis precluded NMR study of organolithium **1d**, which originally had been one of our goals.

Anion **1d** was accordingly generated from the mesitoate ester **7** in the presence of three carbonyl compounds: the unhindered ketones acetone and cyclohexanone and the hindered aldehyde 2,2-dimethylpropanal. The results of these reactions are summarized in Table I.

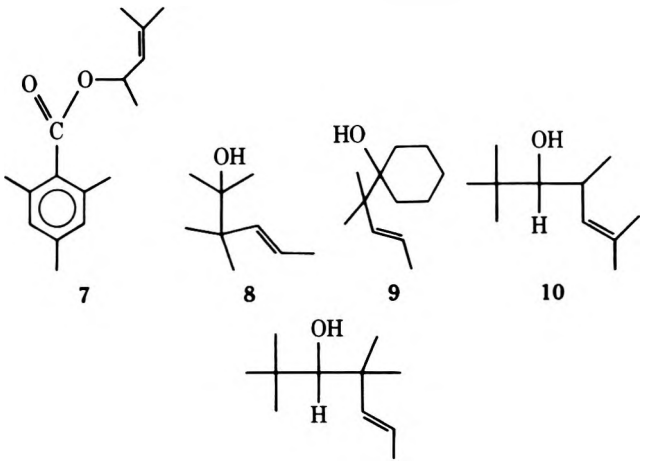


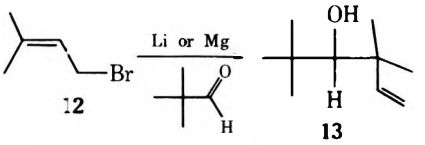
Table I. Reaction of 4-Lithio-2-methyl-2-pentene with Carbonyl Compounds

Registry no.	Carbonyl compd	Products (ratio)	% yield of carbinol(s)
67-64-1	Acetone	**8**	49
108-94-1	Cyclohexanone	**9**	35
630-19-3	2,2-Dimethylpropanal	**10, 11** (1:2)	83

It is interesting to note that reaction of anion **1d** with the unhindered ketones acetone and cyclohexanone gave carbinol products **8** and **9**, respectively, in which the allylic system is attached by the *most* substituted end of the system (γ carbon). This similarity of behavior with the 1-butenyl and 2-methyl-2-butenyl systems which also react with unhindered ketones to produce carbinols in which the allylic system is attached by the γ carbon *may* indicate that the organometallic reagent **1d** has the lithium atom attached to the *least* substituted end of the allylic system (α carbon).

Reaction of **1d** with the more hindered substrate 2,2-dimethylpropanal gave slightly different results. It can be seen in Table I that one of the reaction products, compound **10**, has the allylic unit attached by the *least* substituted end (α carbon) of the allylic system. This type of behavior is similar to that reported by Benkeser and co-workers for the reaction of crotyl Grignard (**1a**) with the very hindered carbonyl electrophile di-*tert*-butyl ketone.[10] These workers reported that although the most rapidly formed (least stable) product had the butenyl (crotyl) system attached by the most substituted end of the allylic system (δ carbon), the more stable product had the allylic unit attached by the least substituted end of the system (α carbon).[11] The product ratio was found to change with time, with the least stable product disappearing almost entirely after 192 h. In the reaction of **1d** with 2,2-dimethylpropanal, the ratio of products **10** and **11** always was 1:2, respectively, regardless of when the reaction mixture was examined. Isolation of pure **10** followed by treatment with lithium metal in tetrahydrofuran led in a very short period of time to a 1:2 mixture of **10** and **11**. This indicates that the product ratio observed is a result of thermodynamic as opposed to kinetic control; the establishment of equilibrium must be extremely rapid.

In contrast to anion **1d**, the 2-methyl-2-butenyl anion (**1b**) can be generated in the presence of 2,2-dimethylpropanal from the corresponding bromide (**12**) using either magnesium[11] or lithium[12] metal. When this was done, the only product found was 3,3,5,5-tetramethyl-1-hexen-4-ol (**13**) in which the allylic



unit is attached by the *most* substituted end (γ carbon) of the allylic system. This would indicate that the behavior observed for anion **1d** and 2,2-dimethylpropanal is due to increased steric hindrance in the more highly substituted allylic anion **1d**.

We have assigned *E* (trans) geometry to the double bond in carbinols **8** and **9** as well as compound **11**. Examination of the vinyl region of the NMR spectrum of these compounds showed a coupling constant for the vinyl protons of 12.5 Hz, a value which makes it difficult to assign geometry. However, strong infrared absorption in the 960–985-cm^{-1} region indicated that the samples were *E* isomers. If the transition state leading to the carbinol product resembles the product itself, then the preference for trans geometry is clear as that geometry in products **8**, **9**, and **11** should result in a more thermodynamically stable product than would cis geometry.

Experimental Section

General. 2-Methyl-2-penten-4-ol (**3**) was prepared by lithium aluminum hydride reduction of mesityl oxide in dry tetrahydrofuran. The alcohol was purified by distillation (137–139 °C, 747 Torr). Mesitoyl chloride was prepared by treating mesitoic acid with thionyl chloride.[13] 2,2-Dimethylpropanal and 2-methyl-4-bromo-2-butene (**12**) were purchased from Chemical Samples Co. Lithium wire (0.1% Na) was obtained from Ventron and was washed in hexane prior to use.

All NMR spectra were recorded on a Varian T-60 instrument with Me_4Si as an internal standard. Ir spectra were recorded on a Beckman IR-8. Microanalyses were performed by the University of Illinois. All preparative gas chromatography was done on a column of 15% Carbowax 20M on 60–80 mesh Chromosorb W.

4-(2-Methyl-2-pentenyl) Mesitoate (7). The ester was prepared in 79% yield from alcohol **3** and mesitoyl chloride:[9] bp 124–126 °C (0.13 Torr); ir (neat) 2980 (m), 2940 (m), 1755 (s), 1630 (m), 1450 (m),

1380 (m), 1272 (s), 1175 (s), 1088 (s), 855 cm^{-1} (m); NMR (CCl_4) δ 1.30 (d, J = 6 Hz, 3 H), 1.78 (m, 6 H), 2.22 (s, 9 H), 5.20 (d, J = 10 Hz, 1 H, vinyl), 5.50–6.05 (m, 1 H), 6.70 (s, 2 H, aromatic).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 77.99; H, 9.00. Found: C, 77.86; H, 8.93.

Reaction of Mesitoate Ester 7 with Carbonyl Compounds. The ester (0.05 mol) and the carbonyl compound (0.05 mol) were allowed to stir in 50 ml of dry THF with an excess (0.5 mol) of lithium metal. When all of the ester was consumed (TLC), the reaction was quenched and a standard aqueous workup employed to isolate the carbinol product(s). Pure samples were prepared by preparative GLC.

Reaction with Acetone. Compound **8**: 49% yield; ir (neat) 3520 (s), 3020 (w), 2960 (s), 1610 (w), 980 cm^{-1} (s); NMR (CCl_4) δ 1.00 (s, 6 H), 1.07 (s, 6 H), 1.75 (d, J = 5 Hz, 3 H), 4.60 (s, 1 H, –OH), 5.58 (m, 2 H, vinyl).

Anal. Calcd for $C_9H_{18}O$: C, 75.98; H, 12.76. Found: C, 75.83; H, 12.82.

Reaction with Cyclohexanone. Compound **9**: 35% yield; ir (neat) 3500 (s), 3040 (s), 2900 (s), 1630 (m), 1450 (s), 1380 (s), 1320 (m), 1270 (s), 1138 (s), 982 (s), 852 cm^{-1} (m); NMR (CCl_4) δ 1.00 (s, 6 H), 1.47 (s, 10 H), 1.76 (d, J = 5 Hz, 3 H), 2.33 (s, 1 H, –OH), 5.58 (m, 2 H, vinyl).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.04; H, 12.17. Found: C, 78.97; H, 12.08.

Reaction with 2,2-Dimethylpropanal. Compounds **10** and **11**, 83% yield overall, 1:2 ratio, respectively.

Compound **10**: ir (neat) 3500 (s), 2900 (s), 2870 (s), 1670 (s), 1480 (s), 1445 (s), 1360 (s), 1080 (s), 980 (s), 840 cm^{-1} (s); NMR (CCl_4) δ 0.90 (s, 9 H), 1.00 (d, J = 6 Hz, 3 H), 1.40 (s, 1 H, –OH), 1.67 (m, 6 H), 2.20 (m, 1 H), 3.10 (d, J = 3 Hz, 1 H), 5.20 (d, J = 9 Hz, 1 H).

Anal. Calcd for $C_{11}H_{22}O$: C, 77.56; H, 13.03. Found: C, 77.42; H, 12.71.

Compound **11**: ir (neat) 3510 (s), 3045 (m), 2900 (s), 1665 (w), 1460 (s), 1265 (m), 1140 (s), 980 cm^{-1} (s); NMR (CCl_4) δ 0.95 (s, 9 H), 1.10 (s, 6 H), 1.68 (d, J = 4.5 Hz, 3 H), 2.30 (s, 1 H), 3.00 (s, 1 H, –OH), 5.42 (m, 2 H, vinyl).

Anal. Calcd for $C_{11}H_{22}O$: C, 77.56; H, 13.03. Found: C, 77.76; H, 12.82.

3,3,5,5-Tetramethylhexen-4-ol (13). 2,2-Dimethylpropanal (0.05 mol) and 2-methyl-4-bromo-2-butene (**12**, 0.05 mol) were treated in dry THF with an excess of magnesium[11] or lithium.[12] Following a standard aqueous workup, the carbinol product **13** was distilled (109–110 °C, 30 Torr). Yield in both cases was approximately 82%; ir (neat) 3500 (s), 3090 (w), 2970 (s), 2880 (s), 1632 (w), 1480 (m), 1365 (m), 1050 (s), 1005 (s), 987 (s), 905 cm^{-1} (s); NMR (CCl_4) δ 1.00 (s, 9 H), 1.18 (s, 6 H), 2.00 (s, 1 H), 3.08 (s, 1 H, –OH), 4.78–5.10 (m 2 H) 6.02 (d of d, J_a = 19, J_b = 10 Hz, 1 H).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.84; H, 12.91. Found: C, 76.57; H, 12.83.

Acknowledgment. The authors thank Research Corporation for their assistance in the form of a Cottrell College Science Grant.

Registry No.—**1d**, 58602-59-8; **3**, 4325-82-0; **7**, 58602-60-1; **8**, 58602-61-2; **9**, 58602-62-3; **10**, 58602-63-4; **11**, 58602-64-5; **12**, 870-63-3; **13**, 58602-65-6; mesityl oxide, 141-79-7; mesitoyl chloride, 938-18-1.

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Tetrabenzylethylene. An Unusually Sterically Hindered Olefin

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Current interest in the properties of sterically hindered olefins[1] prompts us to report our results with tetrabenzylethylene (**1**). In the course of an attempt to prepare a bromohydroperoxide from **1**, we found that **1** was rather inert to the addition of bromine in carbon tetrachloride.[2] Similarly, **1** was inert to potassium permanganate solution[2] over a 25-min period as well as being inert to 2,4-dinitrobenzenesulfonyl chloride[2] and mercuric acetate.[3] The well-known inertness of tetraphenylethylene[4] is usually attributed solely to resonance stabilization of the olefinic bond. However, in view of the inert behavior of **1**, the steric effect of four phenyl groups in close proximity to the olefinic bond may be sufficient for inert behavior.

In order to assess the steric effects in **1**, the rate of bromination in acetic acid at 24.0 °C was measured by an iodometric method.[5] A second-order rate coefficient of $8.68 \pm 0.29 \times 10^{-4}$ M^{-1} s^{-1} was obtained with the reaction mixture under a nitrogen blanket and protected from light. A considerable amount of rate data obtained by Robertson and co-workers for bromination of olefins under these conditions has been compiled.[6] Most of these rates can be correlated with the Taft polar effect equation (eq 1)

$$\log k = \rho^* \Sigma\sigma^* + a_0 \quad (1)$$

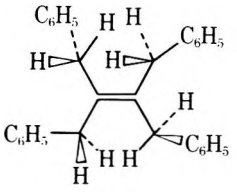
where $\rho^* = -2.58 \pm 0.099$, and $a_0 = 4.85 \pm 0.25$ with r (correlation coefficient) = 0.992. With these values for eq 1, the calculated bromination rate of **1** is 4.28×10^2 M^{-1} s^{-1} at 24 °C. Thus, steric effects in **1** causes a reduction in rate of about 5×10^5-fold ($= 4.28 \times 10^2 / 8.68 \times 10^{-4}$).

Dubois and Mouvier[7] reported the rates of bromination of olefins in methanol at 25 °C with 0.2 M sodium bromide, where steric effects in a few olefins were significant. These data are best correlated with the Taft polar–steric effect equation (eq 2)

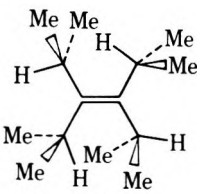
$$\log k = \rho^* \Sigma\sigma^* + \delta \Sigma E_s + a_0 \quad (2)$$

where $\rho^* = -5.30$, $\delta = 0.913$, and $a_0 = 5.64$ with $r = 0.999$.[8] To compare our data in acetic acid at 24 °C to the data of Dubois and co-workers in methanol at 25 °C, we have calculated the relative rate of bromination of **1** in methanol (1.52×10^3 M^{-1} s^{-1}) to acetic acid (4.28×10^2 M^{-1} s^{-1}) where polar effects alone correlate the data.[8] With this factor ($1.52 \times 10^3 / 4.28 \times 10^2 = 3.55$), our experimental rate coefficient in acetic acid becomes 3.08×10^3 M^{-1} s^{-1} ($= 3.55 \times 8.68 \times 10^{-4}$ M^{-1} s^{-1}) in methanol. Now a calculated value of the rate of bromination of **1**, with eq 2 and the parameters from the data of Dubois and Mouvier,[7] is 4.91×10^{-1} M^{-1} s^{-1}. The experimental rate for **1** is then about 160-fold slower than predicted ($4.91 \times 10^{-1} / 3.08 \times 10^{-3} = 160$). Inclusion of **1** into a correlation of the data of Dubois and Mouvier[7] by eq 2 gives a larger δ value; $\rho^* = -6.55$, $\delta = 1.41$, and $a_a = 5.70$ with $r = 0.990$. This may be a more reliable correlation, since it extends the range of E_S values of the olefins by including **1**.[9]

An examination of space-filling molecular models suggests that **1a** is a low-energy conformation of tetrabenzylethylene. Previously, ^1H NMR studies of tetraisopropylethylene indicated a "cogwheel" effect with a high barrier to rotation, which involved conformation **2**.[1] Two distinct tertiary protons were observed due to their disposition about the olefinic bond. Since conformation **1a** suggests unique protons, the ^1H NMR

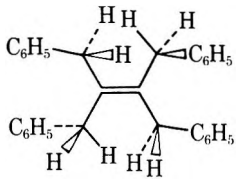


1a



2

spectrum of 1 was measured from approximately 30 to −30 °C in carbon tetrachloride solution. Over this temperature range, the benzyl protons of 1 remained as a singlet. This suggests that the "cogwheel" effect is inoperative with 1. Instead, it seems most reasonable that a rapid equilibrium may occur between conformations 1a and 1b such that unique protons are not detected over this temperature range.



1b

In summary, the bromination rate of 1 dramatically demonstrates the importance of steric effects in addition reactions of olefins.[9] Without a consideration of steric effects, the experimental rate is slower by a factor of about 5×10^5-fold. However, an excellent correlation[11] by eq 2 results when steric effects are included. It is apparent that the mere proximity of phenyl groups to the olefin bond is sufficient to cause slow rates of addition reactions. Lastly, ^{1}H NMR data suggest that a "cogwheel" effect is not operative with 1.

Experimental Section[12]

2,3-Dibenzyl-1,4-diphenyl-2,3-butanediol (3). A mixture of 9.95 g (47.3) mmol) of dibenzyl ketone (MCB, recrystallized from cyclohexane), 0.540 g (20.0 mg-atoms) of aluminum foil (Reynolds Wrap, sanded prior to use), 0.10 g (0.368 mmol) of mercuric chloride, and 150 ml of benzene (reagent grade, distilled from calcium hydride) was stirred and heated at 60–70 °C for 24 h under a nitrogen atmosphere. The reaction mixture was then cooled in an ice bath while 100 ml of 5% hydrochloric acid was added over a 2.0-h period. The organic layer was separated and the aqueous phase was extracted with carbon. tetrachloride. The combined organic phases were washed with water, dried over anhydrous potassium carbonate, and concentrated on a rotary evaporator to give 9.34 g of a viscous yellow oil. NMR analysis of this oil, relative to a measured amount of methylene chloride, indicated a 48% yield of pinacol 3. Chromatography of the oil (9.3 g) on silica gel (70 g) with 10% benzene–90% *n*-hexane eluent gave 4.23 g (42.3% yield) of 3: mp 118–120 °C (lit.[13] mp 120 °C); ir 3560, 3090, 3060, 3030, and 2940 cm^{-1}; NMR OH (1.77, s, 1.94), $C_6H_5CH_2$ [2.92, AB (J = 14 Hz), 8.0], and C_6H_5 (7.08, s, 19.6).

Tetrabenzylethylene (1). A solution of 9.09 g (21.5 mmol) of pinacol 3, 15.0 ml (13.5 g, 90.9 mmol) of ethyl orthoformate (dried over calcium sulfate and distilled at 146 °C), and 0.10 g (0.82 mmol) of benzoic acid was stirred and heated at 148–155 °C (internal temperature) for 9.0 h under a nitrogen atmosphere. During this period 2.0 ml (ca. 80% of theory) of ethanol was distilled from the reaction solution. The excess ethyl orthoformate was distilled and the residual oil was heated with 0.20 g (1.6 mmol) of benzoic acid for 16 h. The reaction mixture was then dissolved in 25 ml of carbon tetrachloride and this solution was washed with 0.2 M potassium carbonate and with water. The organic solution was dried over calcium sulfate and rotary evaporated to 8.31 g of a yellow, oily solid. Recrystallization from *n*-hexane gave 6.60 g (82.8% yield) of white needles of 1: mp 119.7–120.7 °C (lit.[14] mp 119.5–120.5 °C); ir 3080, 3060, 3025, 2960, 2920, and 2850 cm^{-1}; NMR CH_2 (3.47, s, 8.00), C_6H_5 (7.10, s, 20.0); mass spectrum, P m/e 388 (12), P − $C_6H_5CH_2$ 297 (9.0), P − ($C_6H_5CH_2$, C_6H_5, and H) 219 (12), P − [2($C_6H_5CH_2$) and H] 205 (13), P − [2($C_6H_5CH_2$), H, and C] 193 (3.9), and $C_7H_7^+$ 91 (100).

Kinetics of Bromination. An acetic acid solution of 1 and bromine (each 7.63×10^{-3} M) were placed in an aluminum foil wrapped vessel under a nitrogen atmosphere, which was thermostated at 24.0 °C. Aliquots were periodically withdrawn and titrated by an iodometric procedure.[5] The second-order rate coefficients were obtained by a least-squares fit.

Acknowledgment. We thank the U.S. Army Research Office (Durham) for support of this research.

Registry No.—1, 19754-02-0; 3, 33574-71-9; dibenzyl ketone, 102-04-5.

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(9) The bromination of additional olefins, where steric effects are greater, have been reported by Grosjean, Mouvier, and Dubois. A correlation according to eq 2 is mentioned. These data are reported in an abstract, where numerical values are not included.[10]
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Remote Substituent Effects on Carbon-13 Shieldings in Some Bicyclo[2.2.2]octyl Systems

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Fluorine-19 chemical shifts of certain dibenzobicyclo[2.2.2]octyl derivatives, e.g., adducts of 10-substituted 9-fluoroanthracenes with maleic anhydride (I) and dimethyl acetylenedicarboxylate (II), have been studied in anticipation that these ^{19}F substituent chemical shifts (^{19}F SCS) might approximate to the field component of the overall ^{19}F SCS in aromatic fluorides where direct partitioning of components is impossible.[2] Although structural deformations in some bicyclic tertiary fluorides are apparently to blame for worrying fluctuations in chemical shift, Anderson and Stock reasoned

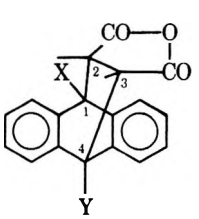
Table I. Carbon-13 Chemical Shifts[a] of Some Bicyclo[2.2.2]octyl Systems

		Carbon number[b]				Substituent effects at carbon			
	System	1	2	3	4	1	2	3	4
III[c]	X = H	23.99	26.11	26.11	23.99				
	Br	62.88	37.61	29.14	22.78	38.89	11.50	3.03	−1.21
	F	92.47	31.30	27.38	24.26	68.48	5.19	1.27	0.27
		(185.3)	(18.4)	(9.4)	(3.3)				
IV[d]	X = H[e]	45.5	48.6	48.6	45.5				
	Br[e]	nl	55.94	50.49	45.0		7.34	1.89	−0.5
	F	95.0	51.87	49.56	44.24	49.5	3.27	0.94	−1.26
		(212)	(18.31)	(6.10)	(3.0)				
	CN[e]	47.2	51.52	48.77	44.67	1.7	2.92	0.17	−0.83
	CH_3	nl	52.33	50.00	45.4		3.73	1.4	−0.1
	$COCH_3$	61.07	50.17	49.85	45.96	15.57	1.57	1.25	+0.46
V[f]	X = H	52.60	147.06	147.06	52.6				
	Br	66.73	(142.63	140.58)	49.90	14.13			−2.7
	CN	nl	(143.88	142.25)	50.28				−2.32
	NO_2	nl	(142.5	143.3)	50.60				−2.00
	CH_3	nl	(155.58	142.15)	50.28				−2.32
	$C(CH_3)_3$	68.84	(155.47	145.49)	51.41	16.24			−1.19
VI	X = H	24.58	26.59	32.18	34.13				
	OCH_3	73.60	29.71	33.09	34.13	49.02	3.12	0.91	0.0
	OH	69.57	34.26[g]	33.48[g]	34.26	44.99	7.67	1.30	0.13
	$OCOCH_3$	80.62	30.23	33.09	34.20	56.04	3.64	0.91	0.07
	F	94.50	31.50	33.52	34.20	69.92	4.91	1.34	0.07
		(183.8)	(19.1)	(10.3)	(2.9)				
	Cl	67.42	36.61	33.35	34.20	52.84	10.02	1.17	0.07

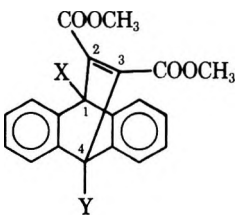
[a] In ppm with respect to internal Me_4Si unless otherwise indicated. Positive shifts correspond to lower shieldings. [b] Numbering system for convenience only. [c] From ref 9 and for CCl_4 solutions referenced to internal cyclohexane. These have been referenced to Me_4Si by assuming δ_c (cyclohexane) is 27.00 ppm. [d] For solvent DMF–$CDCl_3$ (3:1). [e] Confirmed by deuterium substitution. [f] $CDCl_3$ solvent. Assignments for bridging carbons (i.e., C_2, C_3) unproven and β, γ effects therefore not listed. [g] Assignments may require reversal.

that dibenzo fusion should essentially eliminate substituent-induced skeletal changes.[2] These authors suggested, in particular that the ^{19}F SCS data for series II below "portray the polar interactions that would be realised in a rigid molecule such as benzene".

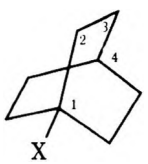
Carbon-13 chemical shifts also seem to provide a useful measure of substituent effects in aromatic systems,[3-8] and again the problem of assessing the field component of the overall ^{13}C SCS arises. Recourse, again, to bicyclic molecules would seem logical but in the study of Maciel and Dorn[9] with 1-substituted bicyclo[2.2.2]octanes (III) it was not clear that the response of C_4 could provide a useful platform from which to develop an understanding of long-range electronic (i.e., δ) effects at carbon. Nevertheless, the proposal of Anderson and Stock[2] regarding the beneficial effects of dibenzofusion seemed to warrant study in respect of carbon-13 shifts. In this note we present our findings for systems IV, V, and VI, and the somewhat melancholy conclusions regarding substituent effects that seem to follow.



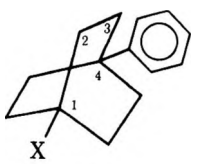
I, Y = F
IV, Y = H



II, Y = F
V, Y = H



III



VI

In this note, we are primarily concerned with the chemical shift of C_4 in series III–VI and spectral assignments have been arrived at by standard techniques. For series IV, C_4 was assigned on the basis of deuterium substitution in the starting anthracenes, consideration of ^{19}F–^{13}C couplings for the fluoroanthracene adduct,[10] and chemical shift trends. For V the closeness of the signals of C_4 and $COOCH_3$ required application of the partially relaxed Fourier transform spectral technique (PRFT),[11] depending on the different relaxation times of such carbons. These assignments for the parent (X = Y = H) of system V were confirmed by a fully proton-coupled spectrum.[10,12] For series VI, C_4 was assigned on the basis of intensities and chemical shifts. The results for C_1–C_4 are presented in Table I. The chemical shifts for other carbons in these systems have generally been obtained, but assignments have not been made, and hence the data are not tabulated.

Regarding the δ effects (i.e., at C_4) it is clear that these are a function of the particular bicyclo[2.2.2]octyl system under scrutiny, although changes in the C_1–C_4 distances are small and not capable of rationalizing these trends through the distance term in the field theory treatment. As suggested by Anderson and Stock,[2] for systems III and IV in particular, structural disturbances are probably significant and may be associated with the quite large variations in some of the α and β effects as well. Nevertheless, in system IV the C_4 SCS are to higher field (except for $COCH_3$), a movement traditionally associated with increased electron density and nuclear shielding.[3-8] For system V, regarded[2] as most resistant to structural unruliness, all C_4 SCS are to higher field by not inconsiderable amounts. The methyl group, which exerts an extremely feeble dipolar effect, is comparable to cyano, nitro, and bromo. The bulky *tert*-butyl group was examined to explore the effect of sterically induced distortions, and in this case the C_4 SCS is the smallest in an absolute sense. "Peri-type" hydrogen interactions are severe in this system as judged

Table II. Analytical and Spectroscopic Data for Certain Adducts

Series IV				Series V			
	Mp, °C	C	H		Mp, °C	C	H
X = H	257–258	(lit. 258–260)[21]		X = H	160–161	(lit. 160–161)[24]	
Br	252–253	(lit. 253–254)[21]		Br	178–179	60.19	3.76
F	239–240	73.20	3.87			(60.15)	(3.76)
		(73.46)	(3.74)	CN	174–175	72.58	4.44
CN	227–228	75.78	3.81			(73.04)	(4.34)
		(75.78)	(3.66)	NO_2	182–183	66.61	4.19
CH_3	269–270	77.96	4.80			(65.75)	(4.10)
		(78.62)	(4.82)	CH_3	184–185	75.39	5.40
$COCH_3$	259–260	75.30	4.51			(75.45)	(5.39)
		(75.47)	(4.40)	$C(CH_3)_3$	177–178	76.40	6.45
						(76.59)	(6.38)

^1H NMR Data

Series V

X =	$-COOCH_3$	CH	Aromatics	Other
H	3.75	5.45	6.85–7.5	
Br	3.77, 3.85	5.70	7.00–7.35	
CN	3.80, 3.91	5.67	7.05–7.35	
NO_2	3.77, 3.84	5.63	7.00–7.35	
CH_3	3.73, 3.80	5.62	6.85–7.5	2.16
$C(CH_3)_3$	3.70, 3.73	5.52	6.96 (m, 4 H) 7.30 (m, 2 H); 7.75 (m, 2 H)	1.82 (6 H); 1.94 (3 H)

Series IV

X =	H_1	H_2	H_3	H_4	Aromatics	Other
H[a]	4.94	3.62	3.62	4.94	7.16–7.60	
$COCH_3$		4.24 ($J_{H_2-H_3}$ = 10 Hz)	3.64 ($J_{H_2-H_3}$ = 10 Hz; $J_{H_3-H_4}$ = 3.5 Hz)	4.90 ($J_{H_3-H_4}$ = 3.35 Hz)	7.2–7.70	2.94
F[a]		3.72	3.66	4.80	7.16–7.68	

[a] Poorly soluble and coupling constants poorly defined.

by the duality of sharp signals in the ^1H and ^{13}C spectra for the methyl groups of the arrested *tert*-butyl group.[13] In system V, the upfield C_4 SCS may be due in part, for the bromo, cyano, and nitro groups, to polarization of the C_4–H σ bond, but "through-space" effects in bicyclo[2.2.2]octyl systems are apparently of secondary importance to "through-bond" effects.[14,15] The reverse may be the situation for the bicyclo-[2.2.1]heptyl framework.[16] In system V, through-bond hyperconjugative transfer of electron density induced by the substituent may occur, but it is not clear what effects on the C_4 chemical shifts it might have.

For system VII, Anderson and Stock[2] observed low-field (i.e., positive) ^{19}F SCS but the correspondence among the substituents for the ^{13}C and ^{19}F SCS is poor. The ^1H chemical shifts of H_4 in system V (these appear as singlets at ca. δ 5.60) are all to lower field from the parent (X = H), with the bromo compound showing the largest shift (+0.25 ppm) and the *tert*-butyl the smallest (+0.07 ppm). Somewhat surprisingly, in system VI, C_4 responds very feebly to 1 substitution and tentatively we associate this with the inability of the substituent to polarize the C_4–phenyl bond, in a direction disfavored on electronegativity grounds. Other poorly understood factors may also be involved.

What are the implications of these results for the idea that SCS data from bicyclic systems approximate to the field component of the overall SCS in substituted aromatics? A number of points warrant emphasis.

(a) For ^{13}C shifts, apparently in systems (e.g., V) regarded as quite rigid, a number of factors, not necessarily related to the electronic capabilities of the substituent, contribute to the overall screening term and vary with the substituent.

(b) While system V may minimize these effects, the presence of highly polar groups in the bridge systems of IV and V may promote varying interactions when the substituents are powerfully dipolar and lead to additional complications. The π nature of the bridging group in V may also sustain certain polarizations.

(c) The recent conclusions[14–16] that in certain bicyclo[2.2.2]octyl systems through-bond transfer of charge, involving the bridging 2,3 bond is important, creates a mechanism for affecting both ^{13}C and ^{19}F SCS in these systems, that is not a complication in benzenoid frameworks. Relating data from the two systems must therefore be somewhat dangerous.

(d) While the results of Anderson and Stock[2] for system II are in the anticipated low-field direction (e.g., when X = NO_2 SCS = 1.68 ppm for DMF) this figure conceivably could be the result of deshielding and shielding contributions, the latter varying in some way with the substituent. The characteristics of the "molecular cavities" in bicyclic and aromatic systems are also different and could seriously affect transmission. See c above.

(e) A crucial assumption for both ^{13}C SCS and ^{19}F SCS would be required that, for example, the response of sp^3-bound fluorine (in system II) to remote dipolar substituents would be similar to the response of sp^2-bound (i.e., aromatic) fluorine. Considering that C–F π-polarization is extremely

important in regulating the ^{19}F chemical shift,[17] the above assumption seems to us to be very tenuous.

(f) Surely the logical approach for magnetic resonance investigation of the field component of the total SCS observed in an aromatic system (whether ^{19}F or ^{13}C) is to examine a system in which the probe nucleus is still in the aromatic environment, but the substituent is contained in an attached, desirably strain-free system, so constructed that resonance and related effects are prohibited. We have seen above that in system V, dipolar substituents actually shield C_4 but in aromatic systems, the whole π system is polarized, and leads to a deshielding of the carbon probe.[18]

The data in Table I indicate wide variations for the α, β, and γ effects as a function of substituent and molecular system.[19] For the α effect there appears to be a basic correlation with substituent electronegativity within a system, but substantial differences between systems for the same substituent, e.g., for the sterically small fluoro, α effects of +68.48 (III), +49.5 (IV), and +69.92 (VI) are noted. The β effects are again positive, i.e., deshielding in nature, but the dependence on substituent electronegativity is not obvious. It would seem in fact, that more electronegative substituents may be associated in part with increased shielding at C_β, a result in accord with some theoretical work predicting alternation of charge in a σ-bonded framework.[20] Other factors, such as degree of substitution and strain, may be important, the latter particularly at the α position. Small but significant deshielding effects at C_γ are also observed, and these C_γ positions are anti to the substituent. It is not clear how well the alternating polarization hypothesis accommodates these data, but a number of factors are almost certainly operating in this region.

Experimental Section

Compounds. The maleic anhydride adducts (series IV) were prepared in the standard way by refluxing the 9-substituted anthracene with slightly more than 1 equiv of maleic anhydride in the minimum amount of o-xylene for 3–12 h, depending on the 9-substituent.[21] On cooling crystals of the adducts separated, in quite pure form, and one further crystallization from xylene provided analytically pure compounds.

9,10-Dideuterioanthracene was obtained by the *p*-toluenesulfonic acid catalyzed H–D exchange with anthracene. Specifically 9-deuterated anthracene resulted from lithium aluminum deuteride reduction of anthrone followed by acid (3 N HCl) induced dehydration. ^1H NMR analysis indicated ~95% deuterium incorporation. 9-Bromo-10-deuterioanthracene was synthesized by bromine addition and hydrogen bromide elimination in the reported manner.[22] Careful ^1H NMR measurements revealed ca. 50% deuterium at the 10 position indicating the absence of a significant isotope effect in the elimination. 9-Cyano-10-deuterioanthracene was obtained from the 9-bromo compound on treatment with copper(I) cyanide in *N,N*-dimethylformamide.[23]

The dimethyl acetylenedicarboxylate adducts (series V)[24] were prepared by refluxing equimolar amounts of the reagents in benzene and monitoring the reaction by ^1H NMR analysis of the $COOCH_3$ region. The benzene solvent was removed and the adducts were recrystallized from methanol. The structures of the adducts were confirmed by elemental analyses, ^1H NMR spectra (where solubility was adequate), and of course the ^{13}C spectra.

Compounds in series I, II, and III have been reported elsewhere,[2,9] while those in series VI will be described in detail in another connection.[25]

^{13}C spectra were recorded with a Bruker HX-90 spectrometer operating in the FT mode, and chemical shifts are relative to internal Me_4Si and accurate to ±0.05 ppm.

The analytical data for new compounds are assembled in Table II, and the ^1H NMR data for series V also. These adducts are generally quite soluble, and the chemical shifts ($CDCl_3$, internal Me_4Si) pertain to 5% weight/volume solutions. The maleic anhydride adducts are far less soluble, and chemical shift data for series IV, X = H, F, and $COCH_3$, only, are tabulated.

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Registry No.—III (X = H), 280-33-1; III (X = Br), 7697-09-8; III (X = F), 20277-22-9; IV (X = H), 5443-16-3; IV (X = Br), 58802-01-0; IV (X = F), 26306-24-1; IV (X = CN), 58802-02-1; IV (X = Me), 58802-03-2; IV (X = $COCH_3$), 17478-86-3; V (X = H), 1625-82-7; V (X = Br), 58802-04-3; V (X = CN), 58802-05-4; V (X = NO_2), 58802-06-5; V (X = CH_3), 58802-07-6; V (X = $C(CH_3)_3$), 33740-56-6; VI (X = H), 23062-62-6; VI (X = OMe), 6555-88-0; VI (X = OH), 2001-62-9; VI (X = OCOMe), 54986-35-5; VI (X = F), 22947-58-6; VI (X = Cl), 33732-68-2.

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A Method for Relating Esterification Rates and Structures of Alkyl-Substituted Acetic Acids

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The relationship between the esterification rate and structure of aliphatic acids has been investigated since the latter part of the 19th century.[1] The collection of data by Loening, Garrett, and Newman[2] for hydrogen chloride catalyzed esterifications in methanol is commonly used in relating structure and rate. By including additional data, some recent studies have suggested that there are relationships between rate and structure not previously disclosed.[3] The purpose of the present study is to further examine the problem of rate and structure by the use of an expanded collection of comparable esterification data.

In the original method the determination of rate coefficients of slow-reacting acids was seriously limited since during the extended esterification time a substantial amount of the hydrogen chloride catalyst reacted with the methanol.[2] In the present study, pairs of acids are allowed to react together and the ratios of the rate coefficients are determined by gas–liquid

Table I. Source and Purity of the Acids and Experimental Results

Registry no.	Acid no.	Structure	Source of acid or precursor	$NE_{calcd} - NE_{found}$	GLC % area	"Known" acid	$k_{known}/k_{unknown} \pm$ std dev
503-74-2	1[a]	$(CH_3)_2CHCH_2COOH$	Eastman Organic	−0.5	98.3		
105-43-1	2	$CH_3CH_2CH(CH_3)CH_2COOH$	K & K	0.3	98.1	1	1.2360 ± 0.0218
97-61-0	3	$CH_3CH_2CH_2CH(CH_3)COOH$	K & K	−0.5	98.5	1	1.4950 ± 0.1422
1070-83-3	4	$(CH_3)_3CCH_2COOH$	Aldrich	1.0	99.0	14	0.3840 ± 0.0520
88-09-5	5	$(CH_3CH_2)_2CHCOOH$	Eastman Organic	−0.9	99.1	14	0.7994 ± 0.0200
14287-61-7	6	$(CH_3)_2CHCH(CH_3)COOH$	K & K	−1.5	96.7	14	0.6773 ± 0.0259
595-37-9	7	$CH_3CH_2C(CH_3)_2COOH$	K & K	−1.3	98.6	14	1.3263 ± 0.1168
32444-32-9	8[a-c]	$(CH_3)_2CHCH(C_2H_5)COOH$	Eastman Organic	1.2	98.1		
19889-37-3	9	$CH_3CH_2C(C_2H_5)(CH_3)COOH$	Chemical Samples	−0.4	99.8	8	1.7825 ± 0.1805
3302-09-8	10[c,d]	$(CH_3)_3CCH_2CH(CH_3)COOH$	Pfautz and Bauer	−0.5	99.6	14	0.2942 ± 0.0137
						14	0.2980 ± 0.0071[e]
149-57-5	11	$CH_3CH_2CH_2CH_2CH(C_2H_5)COOH$	Baker Chemical	−0.4	99.6	15	0.3461 ± 0.0162[f]
813-72-9	12[g]	$CH_3CH_2CH_2CH_2C(CH_3)_2COOH$	K & K	−0.9	95.7	14	1.3456 ± 0.0208
108-81-6	13	$(CH_3)_2CHCH_2CH(C_2H_5)COOH$	Pfautz and Bauer	−0.6	99.1	14	1.1261 ± 0.0924
99-66-1	14[a]	$(CH_3CH_2CH_2)_2CHCOOH$	K & K	−0.5	99.3		
866-72-8	15[g]	$(CH_3)_2CHCH_2C(CH_3)_2COOH$	Pfautz and Bauer	−2.3	98.6	14	2.4691 ± 0.2055
813-58-1	16[c]	$(CH_3CH_2)_3CCOOH$	K & K	−2.4	99.3	9	14.20 ± 4.10
						8	25.61 ± 1.48[e]
						8	25.0[h]
32118-53-9	17[i]	$[(CH_3)_2CH]_2CHCOOH$	Pfautz and Bauer	0.2	94.5	16	2.053 ± 0.031[e,f]
						18	0.827 ± 0.043[e,f]
6967-84-6	18[c]	$(CH_3)_3CCH(C_2H_5)COOH$	Dow Chemical	0.0	99.7	16	2.385 ± 0.431
						16	2.551 ± 0.144[e]

[a] Used as a "known" acid having the value given in ref 2. [b] Prepared by alkaline permanganate oxidation of the aldehyde. [c] The nmr spectra is in agreement with the designated structure. [d] Prepared by periodate–permanganate oxidation of 3,5,5-trimethyl-1-hexene. [e] GLC analysis of both acids and esters. [f] Esterification experiment carried out with each acid in a separate container. [g] Prepared by alkaline permanganate oxidation of the alcohol. [h] Esterification experiment carried out under the conditions given in ref 2. [i] Prepared from isobutyroin, A. A. Sacks and J. G. Aston, *J. Am. Chem. Soc.*, **73**, 3902 (1951).

chromatographic analysis. This method should not be influenced by change in concentration of the catalyst.

The experimental results giving the relative esterification rates of the various pairs of acids are shown in Table I. In determining these relative rates, one of the acids in each pair is considered to have a known rate. Therefore, the value for the "unknown" acid can be calculated. Several acids were used as "knowns" having the rate values given in the collected data of Loening, Garrett, and Newman.

For an examination of the relationship between structure and esterification rates, it was found extremely useful to represent the structure of an acid as a series of digits to be called the "carbon–carbon bond number pattern". Each digit represents the position of a carbon atom in relation to the number of carbon–carbon bonds to the carboxyl group. For example, the carbon–carbon bond number pattern for structure $CH_3CH_2C(CH_3)_2COOH$ is 32221. There are cases, of course, where several acid isomers have the same pattern. All rate data are given as relative to that of butanoic acid and the higher molecular weight normal acids. This is convenient because these acids have essentially the same rate. Examination of the relative rates and the carbon–carbon bond number patterns of acids from the collected data of ref 2 and from this study has led to the proposal of five simple rules for ranking the rate of the acids:

1. If the patterns are the same, the rates are approximately the same.
2. If the patterns for two isomers differ in the value of only one digit, the acid with the lower digit has the slower rate.
3. The acid with the greater combined number of "2's" and "3's" has the slower rate.
4. An acid has a faster or equal rate if its pattern is included in that of another.
5. For acids that cannot be ranked by these rules, the one with the greater number of "2's" has the slower rate.

Although some of these "rules" may seem quite simple, together they form a powerful tool for ranking the rates of the acids. In Table II, the acids have been ranked according to these five rules. The excellent agreement between the ranking by the patterns and experimentally determined values is obvious from inspection of the first two columns. A rank correlation of 0.99 is obtained from this data. Members of a group of acids with the same pattern (five pairs) or undifferentiated by any of the rules (one pair) are given the mean value of the ranks. Values determined in this study are given precedence over those of the collected data. A serious discrepancy occurs in the values for 2,2-diethylbutanoic acid, the last entry in Table II, where the value determined in the present study is only one-seventh of that previously reported. Therefore, several rate coefficients were determined by the method used

Table II. Aliphatic Acids Ranked with Respect to the Carbon–Carbon Bond Number Pattern Rules and the Experimentally Determined Relative Esterification Rates

Rank according to C–C bond no. pattern rules	Exptl detd rel rates	Structure	Carbon–carbon bond no. pattern	Rel esterification rate, 40 °C	
				Coll data (ref 2)	This report
1	1	CH_3COOH	1	2.02	
2	2	CH_3CH_2COOH	21	1.70	
3	3	$H(CH_2)_nCOOH$ ($n > 2$)	$n..321$	1.00	
4	4	$(CH_3)_2CHCH_2CH_2COOH$	44321	0.972	
5.5	5	$(CH_3)_3CCH_2CH_2COOH$	444321	0.937	
5.5	8	$(CH_3)_3CCH(C_2H_5)CH_2CH_2COOH$	555544321	0.206	
7	6	$(CH_3)_2CHCOOH$	221	0.675	
8	7	$(CH_3)_2CHCH_2COOH$	3321	0.236	(0.236)
9	10	$CH_3CH_2CH(CH_3)CH_2COOH$	43321		0.191
10	9	$CH_3CH_2CH(CH_3)COOH$	3221	0.201	
11	11	$CH_3CH_2CH_2CH(CH_3)COOH$	43221		0.158
12	13	$(CH_3)_3CCH_2CH(CH_3)COOH$	4443221	0.0311	0.0632
13	12	$(CH_3)_3CCOOH$	2221	0.0756	
14	14	$(CH_3)_3CCH_2COOH$	33321	0.0474	0.0487
15.5	15	$(CH_3)_2CHCH(CH_3)COOH$	33221		0.0276
15.5	16	$(CH_3CH_2)_2CHCOOH$	33221	0.0202	0.0234
17	17	$CH_3CH_2CH_2CH_2CH(C_2H_5)$-COOH	5433221		0.0219
18.5	18	$(CH_3CH_2CH_2)_2CHCOOH$	4433221	0.0187	(0.0187)
18.5	20	$(CH_3)_2CHCH_2CH(C_2H_5)COOH$	4433221		0.0166
20	19	$(n\text{-}C_4H_9)_2CHCOOH$	554433221	0.0169	
21	23	$[(CH_3)_2CHCH_2]_2CHCOOH$	444433221	0.00839	
22	26	$[(CH_3)_3CCH_2]_2CHCOOH$	44444433221	0.00176	
23	21	$CH_3CH_2C(CH_3)_2COOH$	32221		0.0141
24	22	$CH_3CH_2CH_2CH_2C(CH_3)_2COOH$	5432221		0.0139
25	24	$(CH_3)_2CHCH_2C(CH_3)_2COOH$	4432221		0.00758
26	25	$(CH_3)_3CCH_2C(CH_3)_2COOH$	44432221	0.00667	
27.5	27	$(CH_3)_3CCH(CH_3)COOH$	333221	0.00125	
27.5	28	$(CH_3)_2CHCH(C_2H_5)COOH$	333221	0.00120	(0.00120)
29	29	$CH_3CH_2C(C_2H_5)(CH_3)COOH$	332221		0.000673
30.5	32	$[(CH_3)_2CH]_2CHCOOH$	3333221	Too slow	0.0000232
30.5	33	$(CH_3)_3CCH(C_2H_5)COOH$	3333221	Too slow	0.0000192
32.5	30	$(CH_3)_3CC(CH_3)_2COOH$	3332221	0.000261	
32.5	31	$(CH_3CH_2)_3CCOOH$	3332221	0.000328	0.0000474

to derive the previously reported data. The excellent agreement of these determinations with the GLC analyses gives strong support to this smaller value.

This method of ranking the expected relative esterification rates according to the carbon–carbon bond number patterns is, of course, based on the simple idea that the closer to the carboxyl group, the more effective is a group in retarding the rate. The scheme could not have been previously set forth because until quite recently[3b] it was generally accepted that a more distant β-substitution, a "3" in this case, would have more effect in retarding esterification than a nearer α-substitution, a "2". Only in cases of the extremely hindered acids, the last four entries in Table II, does it seem that this previously accepted concept holds true.

Rule 3 is in accord with the findings of Smith and Burn,[4] who reported that the esterification rates of various types of aliphatic acids tend to fall into classes according to the number of α and β substitutions (the number of "2's" and "3's" in the case of the carbon–carbon bond number patterns). However, this observation apparently was not used in any sort of predictive scheme. Instead, Newman's rule of six[2] is still commonly used to correlate rates with structures.[5] Although determined differently, the six-number of an acid amounts to three times the number of "3's" in the pattern. The greater the six-number the slower the predicted rate. Results would be much improved if consideration were given to the sum of the "2's" and "3's", designated here as the "steric hindrance number". For the acids in Table II with molecular weights above that of propionic, the logarithm of the relative rate is plotted vs. the steric hindrance number. The line determined by the least squares method is

$$\log \text{relative rate} = 2.21 - 1.05 \text{ (steric hindrance number)}$$

With the value of 0.36 for the standard error of estimate for the log of the relative rate, accurate predictions are, of course, not expected. However, since the esterification rate tends to be decreased by a factor of 10 when the steric hindrance number is increased by a unit, a rough estimate can be obtained from the following:

$$\text{estimated rate compared to butanoic acid} = 10^{(2 - \text{steric hindrance number})}$$

Two-thirds of the acids in Table II have relative rate values that are within a factor of 2 of the estimated values.

What has been accomplished here is the development of a method whereby aliphatic acids are ranked according to expected relative esterification rates by a simple inspection of the structures. The demonstrated success of this scheme indicates that it is far superior to any presently available.

Experimental Section

Of the 18 acids used in this study, five were synthesized by methods referred to in Table I. Purity is indicated from neutralization equivalents and GLC analysis. Designated structures of several of the acids were substantiated by NMR spectra obtained on a Varian HA-100 spectrometer modified for carbon-13 pulsed Fourier transform op-

eration. The analytical gas–liquid chromatography was carried out on a Beckman GC-4 gas chromatograph equipped with a flame ionization detector which was interfaced with a Perkin-Elmer PEP-1 data processor. The 6 ft × 0.125 in. stainless steel chromatographic column was packed with 20% diethylene glycol adipate polyester and 3% phosphoric acid on 60/80 mesh Gas-Chrom P.

Experimental Procedures. The reaction mixture containing 5 ml of methanol, approximately 0.05 g of each of the two acids, and 0.01 ml of concentrated hydrochloric acid was esterified at 40 ± 0.04 °C. Reaction times ranged from less than 1 h to more than 1 month. The calculation of r, the relative rate, is based on the equation

$$k_1/k_2 = \ln A/\ln B = r$$

where A is the fraction of acid 1 and B the fraction of acid 2 remaining after the partial esterification. Two GLC methods of analysis were used to determine A and B. In the first method, the analyses were carried out with the column at 160 °C. The reaction mixture also contained 0.05 g of methyl myristate as an internal standard. Determinations of A and B are based on the results of two chromatograms, one taken before and one after the partial esterification; for example

$$A = [\text{final acid 1}][\text{initial standard}]/[\text{initial acid 1}][\text{final standard}]$$

where the items in brackets refer to the GLC areas of the components in the chromatograms. Neither hydrolysis of the internal standard nor esterification occurring in the chromatographic system during analysis was found to be significant. For the second GLC analytical method, in which case the acids and esters are analyzed, the temperature of the column was held at 100 °C for 4 min and then programmed to 160 °C over an 8-min period. No internal standard is needed for this method and only the chromatogram of the partly esterified mixture is used to determine A and B; for example

$$A = (\text{acid 1})/[(\text{acid 1}) + c\ (\text{ester 1})]$$

where c is the mole-area correction factor for the acid–ester pair. The correction factor of 0.92, determined for 2-ethylhexanoic acid and methyl 2-ethylhexanoate, was assumed to hold for the five octanoate entries in Table I.

In two cases, as indicated in Table I, the esterification was carried out with each acid in a separate container because the GLC separation of the mixture was not adequate for good analysis. This means that the esterification environment was not exactly the same for each acid because of different amounts of water produced during the reaction. However, the results should not be particularly affected since under the experimental conditions the "wetness" of the alcohol does not greatly increase during the esterification.

How errors in measuring A and B affect the computation of r has been previously considered.[6] In the present case the relative standard deviation in reproducing the chromatographic peaks was found to be about 3%. Although in the first GLC analytical method, the error in r decreases the further the esterification proceeds, data cannot be used where the hydrolysis reaction becomes significant. Therefore acid pairs were chosen with somewhat similar rates and data was taken when the faster reacting component had esterified from 50 to 80%. For the second method of analysis, based on the relative amounts of each acid and its ester in the partly esterified mixture, the extent of esterification has little influence in the computational error of r. Data can therefore be taken during the early stages of the reaction. This advantage over the first method is somewhat offset by the more complex analytical procedure. Most of the esterification experiments were carried out by the first method described. The values of r in Table I are averages from at least four determinations. The relative standard deviation for r averaged 8%.

Esterification rate coefficients for 2-ethyl-3-methylbutanoic acid and 2,2-diethylbutanoic acid were determined by the procedures used in obtaining the data in ref 2. Samples containing 0.5 M carboxylic acid and 0.005 M hydrogen chloride in dry methanol were sealed in glass ampules and kept at 40 ± 0.04 °C for 413 h. Analysis was carried out by acid titrations. The value of k in liters per mole per second for 2-ethyl-3-methylbutanoic acid was 7.47×10^{-5} (7.80×10^{-5} previously reported) and for 2,2-diethylbutanoic acid was 2.99×10^{-6} (21.4×10^{-6} previously reported). The ratio of the two rates as entered in Table I is $7.47 \times 10^{-5}/2.99 \times 10^{-6} = 25.0$.

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Oxidation of Thiols and Disulfides to Sulfonic Acids by Dimethyl Sulfoxide

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The oxidizing ability of dimethyl sulfoxide (Me_2SO) is well known;[1] still, its ability to oxidize organic sulfur compounds to sulfonic acids has received little recognition. Such oxidations would include certain decompositions of Me_2SO in the presence of bromine, hydrogen bromide, or iodine giving, among other products, methanesulfonic acid or its trimethylsulfonium salt.[2] Methanethiol[2a] and the corresponding sulfenic and sulfinic acids[2d] and sulfinyl halides[2b,c] have been suggested as intermediates.

As for specific examples of the oxidation of thiols and disulfides, Toland[3] has described the oxidation of dodecanethiol to dodecanesulfonic acid in the presence of ammonium bromide at temperatures approaching 170 °C; yet, a similar, preparative decomposition of Me_2SO to methanesulfonic acid at 175 °C is also described. Further, Lipton and Bodwell[4] have reported that cystine is oxidized to cysteic acid by minor amounts of Me_2SO under conditions used for the acid-catalyzed hydrolysis of proteins.

The above Me_2SO decompositions also produce paraformaldehyde and dimethyl sulfide (DMS) and may be hazardous.[2a,5] Thus, application of Me_2SO to oxidation of thiols and disulfides has the disadvantage of both hazard and contamination of product sulfonic acid with methanesulfonic acid.

I have now found that, in the presence of a catalytic amount of bromine or iodine or their hydrogen halide, thiols and disulfides may conveniently be oxidized to the corresponding sulfonic acid with little Me_2SO decomposition through the simple expedient of having water present during the oxidation of thiols (eq 1) and excess water present during the oxidation of disulfides (eq 2). With such presence of water, the characteristic deposit of paraformaldehyde in the upper reaches of the reaction vessel is much reduced or absent and reaction occurs in good agreement

$$RSH + 3CH_3SCH_3 \longrightarrow RSO_3H + 3CH_3SCH_3 \quad (1)$$

$$RS{-}SR + 5CH_3SCH_3 + H_2O \longrightarrow 2RSO_3H + 5CH_3SCH_3 \quad (2)$$

Table I. Effect of Water on Oxidations [a]

H_2O/RSH or RSSR, molar ratio	Nature of reaction	Deposit, $(CH_2O)_n$	DMS yield, % theory	Acidity, % theory
	Benzenethiol (1.57 M, at 110 °C)			
0	Rapid and vigorous	Abundant	131	154
0.71	Moderate	Absent	86	107
	Dimethyl Disulfide (1.13 M, at 90 °C)			
1.00	Eventually vigorous	Abundant	183	191
1.44	Gradual	Trace	103	109

[a] 0.0356 M HBr catalyst.

Table II. Effect of Variables on Completion Time in Oxidation of DMDS [a] (1.13 M, HBr Catalyst)

Temp, °C	Water/DMDS molar ratio	Catalyst concn, M	Completion time, h
90	1.44	0.0356	10.75
90	2.00	0.0356	>12
90	4.00	0.142	6.5
100	2.00	0.0356	6.5
100	3.00	0.0712	5
110–120	2.00	0.0178	6.5
110–120	2.00	0.0356	3.25

[a] Dimethyl disulfide.

Table III. Effect of Added Methanesulfonic Acid on Completion Time, Oxidation of DMDS (1.13 M; Water, 2.22 M)

Catalyst (concn, M) [a]	Temp, °C	Added CH_3SO_3H, M	Completion time, h
I_2 (0.0316)	130	None	4.5
I_2 (0.0316)	110	0.40	5
HBr (0.0356)	90	None	Negligible rxn
HBr (0.0356)	90	0.40	⅓ complete in 7

[a] I_2 expressed as HI equivalents.

with theory (reaction 1 or 2) in DMS yield and titratable acidity (Table I).

Chlorine and hydrogen chloride are known to catalyze sulfoxide oxidation of thiols to disulfides,[6] but on checking for further oxidation of disulfides, there was only a slow evolution of DMS. Thus, they do not provide practical catalysis for oxidation to sulfonic acid; though, in the presence of a minor amount of iodine or hydrogen iodide, good catalysis is obtained.

The oxidations are conducted with excess Me_2SO as solvent and at elevated temperatures with distillation of produced DMS so that the progress of the oxidation may be followed. In satisfactory oxidations, completion is indicated by a marked slowing or near cessation of DMS formation at about the theoretical amount. For successful application with negligible Me_2SO decomposition, the concentrations of thiol or disulfide, water, and catalyst and reaction temperature must be adjusted in relation to one another.

Water has a marked moderating effect. As its concentration is increased, the oxidation becomes excessively sluggish, but this may be compensated for by an increase in catalyst concentration or reaction temperature (Table II). However, with increased catalyst concentration and temperature, particularly if not appropriately compensated for with more water, there is a greater probability of Me_2SO decomposition, further oxidation to sulfuric acid and, generally, a more impure product.

An induction period for the formation of DMS is regularly observed. This period can be decreased and oxidation time shortened through the addition of acid, e.g., sulfuric acid, though addition of the same acid as expected from the oxidation is most convenient preparatively. Addition of acid also permits satisfactory oxidation at somewhat lower temperatures (Table III).

The use of a high concentration of thiol or disulfide (about 4.8 and 2.4 M, respectively) resulted in oxidations that were difficult to control. In practice thiol concentration was kept below 2.4 M, and disulfide, below 1.2 M. Bromine–hydrogen bromide catalyzed oxidations were generally conducted at about 110 °C, and iodine–hydrogen iodide catalyzed oxidations at somewhat higher temperatures. Lower temperatures were often suitable where the above catalysts were used in conjunction with HCl or other added acid. The use of high catalyst concentrations and temperatures so as to have short reaction times was avoided. For separation of the product sulfonic acid from excess Me_2SO, the use of ion exclusion chromatography[7] was found to be convenient; though, generally, the reaction mixture was neutralized with aqueous sodium hydroxide and the salt recovered after addition of a precipitant.

The oxidation was applied successfully to a number of aliphatic and aromatic thiols and disulfides. Table IV summarizes these experiments. The method compares favorably with other oxidation procedures.[8] The oxidation of 2-methyl-2-propanethiol and bis(*tert*-butyl) disulfide led to decomposition, and only sodium sulfate was identified after neutralization.

The subject oxidation has much in parallel with the halogen–hydrogen halide catalyzed oxidations of aliphatic thiols to disulfides by sulfoxides.[6] In addition to the same oxidant and catalysts, there is retardation or moderation by water, enhancement of catalysis by addition of a nonhydrohalic acid, and satisfactory mixed chlorine–iodine species catalysis contrasted with inferior chlorine species catalysis. The principal distinction is a higher reaction temperature without a reduced reaction time. Again, reaction 3 accounts for catalysis by both halogen and its hydrogen halide. The produced halogen may play a leading role in the actual oxidation.

$$CH_3\overset{\overset{O}{\|}}{S}CH_3 + 2H^+ + 2X^- \rightleftharpoons CH_3SCH_3 + H_2O + X_2 \quad (3)$$

In view of the greater ease of oxidation of a thiol to its disulfide, the disulfide would appear to be an intermediate in oxidation of thiol to the sulfonic acid. Color changes such as those reported for iodine–hydrogen iodide catalyzed oxidation to disulfide[6] have been observed part way through the oxidation to the sulfonic acid. Thereafter, the mixture retained the amber, iodine color.

I suggest that a further intermediate or intermediates[9] have the structure 1 where X is the halogen species employed as catalyst and that the beneficial role of water is to hydrolyze such intermediates, thereby limiting undesirable reaction with Me_2SO. Such a hydrolysis would also regenerate catalyst. An example of undesirable reaction with Me_2SO is the case of a sulfonyl chloride ($n = 2$).[10] The Me_2SO oxidation of such possible intermediates and their hydrolysis products is presently being investigated.

RSO_nX

1, $n = 0, 1$ or 2

Table IV. Summary of Oxidations to Sulfonic Acid [a]

Registry no.	Thiol or disulfide	Concn, M	Catalyst (M × 10²) [b]	Temp, °C	Rxn time, h	DMS yield % theory	Acidity, % theory [c]	Na sulfonate yield, % [d]	Na_2SO_4 yield, % [e]
624-92-0	Dimethyl	1.126	I_2 (3.16)	130	4.25	89	105	96	<0.1
	Dimethyl	1.126	I_2 (1.58)	130	6.25	90	103		
	Dimethyl	1.126	HI (3.48)	130	4.5	88	104		
	Dimethyl	1.126	Br_2 (3.66)	110	3	90	105		
	Dimethyl	1.126	HBr (3.56)	110	3.25	89	106	92	<0.1
	Dimethyl	1.126	HBr (1.78)	110	6.5	91	103		
	Dimethyl	1.126	HCl (3.60) [f]	100	6.25	81	105	97	<0.1
110-81-6	Diethyl	0.972	I_2 (3.16)	120	6	88	108	84	8
	Diethyl	0.972	HBr (3.56)	110	3.75	85	107	82	0.6
109-79-5	Butane-	1.850	I_2 (3.16)	120	7	86	113	71	20
	Butane-	1.850	HBr (3.56)	110	5.75	92	110	89	4
75-33-2	2-Propane-	1.692	HBr (3.56)	110	7.75 [g]	88	107	90	2.4
	2-Propane-	1.692	HCl (3.60) [f]	110	17 [g]	120	147	44	45
108-98-5	Benzene-	1.568	I_2 (3.16)	130	4.75	85	106	87	Trace
	Benzene-	1.368	HBr (3.56)	110	3.5	83	107	88	Trace
882-33-7	Diphenyl	0.732	I_2 (3.16)	130	3.75	83	108	94	Trace
1155-00-6	Bis(2-nitrophenyl) [h]	0.520 [i]	HBr (7.12)	*j*	7	118	143	90	4.5
	Bis(2-naphthyl)	0.502 [i]	HBr (3.56)	110	4.75	91	130	84 [k]	
5586-15-2	Bis(2-naphthyl)	0.628 [i]	HCl (3.60) [f]	105	4.25	94	117	79 [k]	

[a] Oxidations were conducted in 50 ml of Me_2SO. The water concentration was 1.11 M with thiols and 2.22 M with disulfides except as indicated. [b] Halogen concentrations are expressed as equivalents of hydrogen halide. [c] Based upon the amount of 5 N NaOH solution required to neutralize the reaction mixture. Theory according to reaction 1 or 2, as applicable. [d] Yield of crude product less yield of Na_2SO_4 except as indicated. [e] Based upon thiol or disulfide. [f] Iodine also present, 0.64–0.66 × 10^{-2} M as HI. [g] Temperature of the reaction mixture was gradually increased from 70 to 110 °C in 2–3 h before start of this heating period. [h] Water concentration was 1.11 M. [i] Incompletely soluble initially. Went into solution as the oxidation progressed. [j] See Experimental Section. [k] Yield after recrystallization from water.

Experimental Section

Reagents. The Me_2SO, halogens, and hydrohalic acids were reagent grade. The concentrations of the acids follow: HI, 57%; HBr, 48%; and HCl, 37%. Ordinary quality, commercial thiols and disulfides were used directly when available. Practical grades were redistilled. Bis(2-naphthyl) disulfide was prepared by oxidation of 2-naphthalenethiol.[6]

General Aspects of the Oxidation Procedure. The reactants were heated by means of an oil bath in a flask equipped with a distillation head suitable for collection of DMS. Temperatures were approximate. Such heating was continued until the rate of DMS distillation went through a maximum and slowed to less than about ⅓ ml per 15-min period per 100 mmol of expected sulfonic acid. Unless indicated otherwise, the reaction mixture was neutralized by addition of sodium hydroxide solution. The sodium salt was precipitated (preferably after removal of water under vacuum) by addition of acetone and ethyl acetate (about 200 ml of each per 100 mmol of expected sulfonate). The salt was dried at 130 °C and then recrystallized from ethanol[11] to separate from any sodium sulfate. Recrystallized salt was treated with phosphorus pentachloride and then concentrated aqueous ammonia to obtain the sulfonamide. In each case, the melting point of the sulfonamide agreed with the reported value.[12]

The following experiments are given as examples. Melting and boiling points are uncorrected.

Methanesulfonic Acid. A solution of 15 ml (169 mmol) of DMDS, 6 ml (333 mmol) of water, and 0.60 ml (5.34 mmol) of hydrobromic acid in 150 ml of Me_2SO was heated at 100–110 °C. After a bit, a distillation at 38–45 °C commenced. Heating was continued until the distillation temperature dropped and distillation slowed to less than 1 ml in a 15-min period (about 4.25 h). Distillate (56.5 ml) was obtained and proved to be mainly DMS. It redistilled at 37–39 °C and gave a mercuric chloride derivative melting at 159–161 °C (reported for the DMS derivative, 156–158 °C).[13]

Two-thirds of the reaction mixture was removed, and after dilution with 200 ml of water, the acid pesent was separated from excess Me_2SO by ion exclusion chromatography[7] on Dowex ion exchange resin (50-X8, acid form). The acid fraction was concentrated, then methanesulfonic acid distilled at 1 mm. Obtained was 19.6 g (90% of theory). The melting and boiling points agreed with literature values.

The remaining third of the reaction mixture was neutralized by addition of 24.3 ml of 5 N NaOH. Addition of 250 ml of acetone and 150 ml of ethyl acetate gave 12.4 g of crude sodium methanesulfonate (93% of theory). After recrystallization from 95% alcohol, the melting point was 353–355 °C (reported, 345 °C).[14]

2-Nitrobenzenesulfonic Acid. A mixture of 8.0 g (26.0 mmol) of bis(2-nitrophenyl) disulfide, 1 ml (55.5 mmol) of water, 0.40 ml (3.56 mmol) of hydrobromic acid, and 50 ml of Me_2SO was initially heated at 120 °C, but the temperature was gradually allowed to drop to 106 °C. In 7 h, 11.2 ml of DMS distilled.[15] NaOH (5 N, 15.2 ml) was required to neutralize the residue. After water was removed by heating under vacuum, 200 ml of ethyl acetate was added, and the mixture triturated. This was repeated with 100 ml of fresh ethyl acetate. Crude sodium 2-nitrobenzenesulfonate (10.9 g) was obtained. The yield was 90% after correction for 0.33 g of sodium sulfonate removed by crystallization from 95% alcohol.

Registry No.—Me_2SO, 67-68-5; methanesulfonic acid, 75-75-2; ethanesulfonic acid, 594-45-6; 1-butanesulfonic acid, 2396-47-2; 2-propanesulfonic acid, 14159-48-9; benzenesulfonic acid, 98-11-3; 2-nitrobenzenesulfonic acid, 80-82-0; 2-naphthalenesulfonic acid, 120-18-3.

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(15) Bis(2-nitrophenyl) disulfide was notably resistant to oxidation, and these conditions somewhat pressed the stability limits of Me_2SO. Though distillation of DMS had slowed by 7 h, it was still continuing at more than the usual rate.

Reactions of Fluorodinitroethoxyacetyl Chloride and Fluorodinitroethoxyacetic Anhydride with Friedel–Crafts Catalysts[1]

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Simple aliphatic anhydrides have been reported to react with boron trifluoride to give the symmetrical ketones.[2,3] Simple acid halides and tertiary amines gave ketene dimers, which on hydrolysis gave the corresponding ketones.[4] On the other hand, tertiary carboxylic acids, acid halides, and anhydrides underwent decarbonylation with Friedel–Crafts catalysts;[5] pivalyl chloride and aluminum chloride gave HCl, CO, and isobutylene.[6]

These reactions of fluorodinitroethoxyacetic acid derivatives were investigated as a continuation of our earlier work on this class of compounds.[7,8]

Fluorodinitroethoxyacetic acid and fluorodinitroethoxyacetyl chloride needed for this work were prepared by reported[7] procedures. Fluorodinitroethoxyacetic anhydride, unknown prior to this work, was synthesized in 60% yield by dehydrating fluorodinitroethoxyacetic acid with acetic anhydride:

$$2FC(NO_2)_2CH_2OCH_2CO_2H + (CH_3CO)_2O \xrightarrow[\Delta]{} [FC(NO_2)_2CH_2OCH_2CO]_2O$$

Fluorodinitroacetic anhydride reacted with boron trifluoride under the reaction conditions employed by Man and Hauser.[3] The reaction product, however, was not the expected ketone, but fluorodinitroethoxymethyl fluorodinitroethoxyacetate:

$$[FC(NO_2)_2CH_2OCH_2CO]_2O \xrightarrow{BF_3} FC(NO_2)_2CH_2OCH_2COOCH_2OCH_2CF(NO_2)_2$$

A small amount of fluorodinitroethoxymethyl acetate was also obtained in this reaction.

Fluorodinitroethoxyacetyl chloride reacted readily with triethylamine in ethereal solution to give a white, crystalline solid. The stoichiometry of reaction and the solubility characteristics of this product indicated that instead of the expected ketene dimer, the reaction product was fluorodinitroethoxyacetyl triethylammonium chloride:

$$FC(NO_2)_2CH_2OCH_2COCl + N(C_2H_5)_3 \not\rightarrow FC(NO_2)_2CH_2OCH{=}C{=}O \quad (C{=}O)$$

$$FC(NO_2)_2CH_2OCH_2CON^+(C_2H_5)_3Cl^- \qquad CH_2OCH_2CF(NO_2)_2$$

Unlike the reported reaction of ketene dimers, this material yielded dark, tarry product on treatment with water which did not contain any 1,3-bis(fluorodinitroethoxy)acetone.

Fluorodinitroethoxyacetyl chloride did not react with weak Friedel–Crafts catalysts such as stannic chloride or ferric chloride. The acid chloride, however, reacted rapidly with aluminum chloride with evolution of a gas. The product of this reaction was characterized as the previously reported[9] chloromethyl fluorodinitroethyl ether.

$$FC(NO_2)_2CH_2OCH_2COCl + AlCl_3 \longrightarrow FC(NO_2)_2CH_2OCH_2Cl + CO$$

These results are consistent with the initial reaction of fluorodinitroethoxyacetic anhydride and fluorodinitroethoxyacetyl chloride with Friedel–Crafts catalysts to give fluorodinitroethoxyacylium cation intermediate. Instead of losing the α proton and yielding fluorodinitroethoxyketene as is the case with simple carboxylic acid derivatives, this intermediate undergoes decarbonylation to give fluorodinitroethoxymethyl cation:

$$FC(NO_2)_2CH_2OCH_2COCl \xrightarrow{AlCl_3} [FC(NO_2)_2CH_2OCH_2CO]^+ + Cl^-$$

$$[FC(NO_2)_2CH_2OCH_2CO]_2O \xrightarrow{BF_3} [FC(NO_2)_2CH_2OCH_2CO]^+ + FC(NO_2)_2CH_2OCH_2COO^-$$

$$[FC(NO_2)_2CH_2OCH_2CO]^+ \xrightarrow{-CO} [FC(NO_2)_2CH_2OCH_2]^+$$

Thus, the fluorodinitroethoxy group appears to promote decarbonylation rather than ketene formation because of oxygen stabilization of the resulting cation, $FC(NO_2)_2CH_2OCH_2^+$.

Experimental Section

Fluorodinitroethoxyacetic Anhydride. A solution of 10 g (0.0472 mol) of fluorodinitroethoxyacetic acid[7] in 15 ml of acetic anhydride was refluxed for 8 h and the excess of acetic anhydride and acetic acid were removed under reduced pressure. The reaction product, 8.3 g, was contaminated with fluorodinitroethoxyacetic acid which was removed by distillation at 175–180 °C (0.1 mm). The degassed material amounting to 6.1 g (64% yield) solidified at room temperature and was crystallized from carbon tetrachloride to give 5.1 g of a white, crystalline solid: mp 54 °C; ^{1}H NMR ($CDCl_3$) δ 4.32 (d, J_{HF} = 16 Hz, 4 H, $2FCCH_2-$) and 4.69 ppm (s, 4 H, $2-CH_2CO-$).

Anal. Calcd for $C_8H_8F_2N_4O_{13}$: C, 23.66; H, 1.98. Found: C, 23.42; H, 2.03.

Fluorodinitroethoxymethyl Fluorodinitroethoxyacetate. A slow stream of boron trifluoride was passed at 0 °C for ca. 50 min into a stirred and cooled solution of 4 g (0.01 mol) of fluorodinitroethoxyacetic anhydride in 3 ml of chloroform. The resulting mixture was added to a solution of 4 g of sodium acetate in 9 ml of water and heated at 95–100 °C for 45 min. Chloroform was allowed to evaporate. The cooled mixture was extracted with 25 ml of methylene chloride and the methylene chloride solution was washed with 50 ml of saturated aqueous sodium bicarbonate solution followed by 50 ml of water. The methylene chloride solution was dried and stripped to give 2.2 g of oil. The crude material was distilled at 150 °C (0.1 mm) in a short-path micro distillation apparatus to give 1.9 g of fluorodinitroethoxymethyl fluorodinitroethoxyacetate, a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.25 (s, 2 H, $-COOCH_2O-$), 4.62 and 4.68 (two doublets, $J_{HF} \simeq$ 16 Hz, 4 H, $2FCCH_2-$), and 4.23 ppm (s, 2 H, $-OCH_2COO-$).

Anal. Calcd for $C_7H_8F_2N_4O_{12}$: C, 22.24; H, 2.13. Found: C, 22.36; H, 2.18.

A few drops of a colorless liquid obtained as a forerun in the above distillation was identified as fluorodinitroethoxymethyl acetate: ^{1}H NMR ($CDCl_3$) δ 5.17 (s, 2 H, $-COOCH_2-$), 4.66 (d, J_{HF} = 16 Hz, 2 H, $FCCH_2-$), and 2.10 ppm (s, 3 H, CH_3).

Anal. Calcd for $C_5H_7FN_2O_7$: C, 26.56; H, 3.12. Found: C, 27.3; H, 3.14.

Reaction of Fluorodinitroethoxyacetyl Chloride with Aluminum Chloride. Gas was evolved immediately when 0.3 g of anhydrous aluminum chloride was added to 1.0 g (0.047 mol) of fluorodinitroethoxyacetyl chloride. When evolution of gas ceased in ca. 10 min, the mixture was washed with 10 ml of ice water and extracted with 10 ml of methylene chloride. The methylene chloride solution was distilled to give 0.85 g of a colorless liquid, bp 40 °C (0.2 mm), identified as chloromethyl fluorodinitroethyl ether by comparing its physical properties and its ^{1}H NMR spectrum with those of an authentic sample of the ether.[9] There was no reaction when a 4:1 molar mixture of fluorodinitroethoxyacetyl chloride and stannic chloride

was heated at 95–100 °C for a few hours. Similarly, no reaction occurred when the acid chloride saturated with boron fluoride was allowed to stand at ambient temperature for 4 days.

Reaction of Fluorodinitroethoxyacetyl Chloride with Triethylamine. To a stirred and cooled (0–5 °C) solution of 2.3 g (0.01 mol) of fluorodinitroethoxyacetyl chloride[7] in 70 ml of diethyl ether was added dropwise (15 min) a solution of 1.0 g (0.01 mol) of triethylamine in 15 ml of diethyl ether. A white, crystalline solid precipitated instantaneously. The mixture, protected from moisture by a calcium chloride drying tube, was refluxed for 24 h, cooled, and filtered. The filter cake, washed with ether, amounted to ca. 3 g. The filtrate and washings were combined and evaporated on a rotary evaporator, leaving no residue.

Registry No.—Fluorodinitroethoxyacetic anhydride, 58815-88-6; fluorodinitroethoxyacetic acid, 25172-22-9; fluorodinitroethoxymethyl fluorodinitroethoxyacetate, 58815-89-7; fluorodinitroethoxymethyl acetate, 50836-79-8; fluorodinitroethoxyacetyl chloride, 25172-23-0; aluminum chloride, 7446-70-0; triethylamine, 121-44-8.

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Bromination of 1-Alkyl-3-methyl-2-pyridones with *N*-Bromosuccinimide

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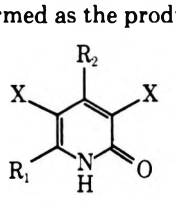
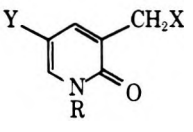
The functionalization of a β-methyl group attached to a pyridine or quinoline ring has proven to be an important step in several approaches to the synthesis of camptothecin[1,2,3] and bromination with *N*-bromosuccinimide (NBS) met with only limited success. With the pyridine derivatives no bromination of the ring or alkyl substituent occurred unless the basicity of the nitrogen was decreased by an electronegative, α substituent.[1,4] With 6-methyl- or 4,6-dimethyl-2-pyridone (**1** or **2**) NBS caused ring bromination to **3** and **4** rather than substitution of the methyl groups even using benzoyl peroxide as catalyst.[5,6] The earlier report[7] that 1,3-dimethyl-2-pyridone (**5**) gave bromination of the 3-methyl group with NBS to give **6** was recently questioned, for ring bromination to give **7** was confirmed as the product from this reaction.[3]



1, $R_1 = CH_3$; $R_2 = X = H$
2, $R_1 = R_2 = CH_3$; $X = H$
3, $R_1 = CH_3$; $R_2 = H$; $X = Br$
4, $R_1 = R_2 = CH_3$; $X = Br$



5, $R = CH_3$; $X = Y = H$
6, $R = CH_3$; $X = Br$; $Y = H$
7, $R = CH_3$; $X = H$; $Y = Br$
8, $R = PhCH_2$; $X = Y = H$
9, $R = PhCH_2$; $X = H$; $Y = Br$
10, $R = PhCH_2$; $X = Br$; $Y = H$

Since 1-substituted 3-bromomethyl-2-pyridone would be a convenient intermediate the NBS reaction with 1-alkyl-3-methyl-2-pyridones (**5** and **8**) was reinvestigated. A dilute solution of 1-benzyl-3-methyl-2-pyridone (**8**) was treated with NBS and dibenzoyl peroxide in refluxing carbon tetrachloride for 50 min and a solid product remained after filtration and evaporation of the solvent. The NMR spectrum of the product showed the triplet at 6.17 ppm due to the aromatic 5 proton, but the singlet at 2.16 ppm due to the signal for the *C*-methyl was missing. A new singlet was evident at 4.47 ppm due to a bromomethylene group. The elemental analyses confirmed that bromination of the methyl group had occurred to give **10**. A careful analysis of the NMR spectrum showed the presence of a trace of starting compound **8** but there were no signals which could be assigned to **9**. The reaction was repeated using the concentration of reagents previously reported to give ring bromination of **5**[3] and again the major product was the bromomethyl derivative **10** with only 20–30% of the ring brominated product **9** detectable by NMR. Indeed a reasonable yield of ring bromination of **8** could be obtained only by a reaction with NBS in the *absence* of dibenzoyl peroxide. In benzene or carbon tetrachloride the NMR of the crude product showed the presence of only about 10% of the bromomethyl derivative **10**.

The reactions were repeated with 1,3-dimethyl-2-pyridone (**5**) and NBS, in the absence of dibenzoyl peroxide or with this catalyst in a concentrated reaction mixture, and gave **7** as the major product by ring bromination. The crude products contained about 10% unreacted **5** and 10% of the 3-bromomethyl-1-methyl-2-pyridine (**6**) detected by NMR analysis. The reaction of **5** with NBS and dibenzoyl peroxide after an eightfold dilution gave mainly side-chain bromination to form **6** contaminated with only a few percent of starting material or product of ring bromination, **7**.

The ring or chain bromination of 1-alkyl-3-methyl-2-pyridones with NBS can be controlled in two examples to give either ring or side chain substitution. In the absence of dibenzoyl peroxide as a catalyst, NBS gave bromination of the ring in the same manner as would be expected with molecular bromine. In the presence of dibenzoyl peroxide, dilute reaction conditions gave side chain bromination with NBS. In concentrated reaction mixtures significant yields of ring bromination occurred even in the presence of dibenzoyl peroxide. The 1-methyl derivative, **5**, was more sensitive to this concentration effect than was the 1-benzyl-3-methyl-2-pyridone (**8**). By a proper choice of reaction conditions selectivity could be controlled to give crude products which crystallized and whose NMR analyses showed less than 10% contamination by the isomeric bromination product.

Experimental Section

1-Benzyl-3-methyl-2-pyridone (8). To a solution of 6.44 g of 87% KOH in 150 ml of absolute ethanol at 50 °C was added 3-methyl-2-pyridone.[8] The resulting solution was stirred for 20 min before the dropwise addition of benzyl chloride. The mixture was stirred at 50 °C for 3 h, concentrated under reduced pressure, poured into 180 ml of water, and extracted with chloroform (3 × 50 ml). The organic phase was washed with water and saturated salt solution, dried ($MgSO_4$), filtered, and concentrated to yield a light yellow oil which crystallized under pentane with cooling. The solid was collected and dried to give 15.75 g (86%) of **8** as white crystals, mp 69–71 °C. The product was recrystallized twice from petroleum ether (bp 30–60 °C)–methylene chloride to afford an analytical sample of **8**: mp 70.5–71.5 °C; NMR ($CDCl_3$) δ 7.12–7.48 (m, including s at 7.36, 7 H total), 6.06 (t, 1 H), 5.15 (s, 2 H), 2.16 (s, 3 H); ir (KBr) 1645 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.34; H, 6.78; N, 7.11.

1,3-Dimethyl-2-pyridone (5). Using the procedure above, 6.94 g (63.6 mmol) of 3-methyl-2-pyridone and 13.0 g (91.6 mmol) of methyl iodide gave after vacuum distillation 6.63 g (85%) of **1** as a clear oil: bp 63 °C (0.05 mm) [lit.[8] bp 83–84 °C (1.3 mm)]; NMR ($CDCl_3$) δ 7.24–7.50 (m, 2 H), 6.16 (t, 1 H), 3.60 (s, 3 H), 2.16 (s, 3 H); ir (neat) 1650 cm^{-1}.

1-Benzyl-5-bromo-3-methyl-2-pyridone (9). A solution of 1.0 g (5.02 mmol) of **8** in 10 ml of dry benzene was placed in a dry, nitrogen-filled flask. To the solution was added 0.90 g (5.02 mmol) of NBS and the mixture was heated at 90 °C for 50 min. The benzene was removed under reduced pressure, 25 ml of carbon tetrachloride was added to the residue, and the resulting mixture was filtered. The filter cake was washed with 25 ml of carbon tetrachloride and the filtrate was concentrated under reduced pressure leaving an orange oil as residue, the NMR of which showed less than 10% of **10**. The oil crystallized on cooling, and trituration with 10 ml of anhydrous ether gave 0.95 g (68%) of crude **9** as a white solid, mp 86.5–89 °C. The solid was recrystallized twice from ether to give an analytical sample of **9**: mp 96.5–97.5 °C; NMR ($CDCl_3$) δ 7.04–7.60 (m, including s at 7.23, 7 H total), 5.02 (s, 2 H), 2.12 (s, 3 H).

Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04. Found: C, 55.98; H, 4.56; N, 5.00.

The reaction in 10 ml of carbon tetrachloride gave identical results. The product crystallized and NMR of the crude solid showed about 10% of **10**.

1-Benzyl-3-bromomethyl-2-pyridone (10). In a 100-ml flask equipped with a reflux condenser and a drying tube was placed a solution of 1.0 g (5.02 mmol) of **8** in 75 ml of dry carbon tetrachloride. To the solution was added 0.90 g (5.02 mmol) of NBS and 0.1 g of dibenzoyl peroxide. The mixture was heated under reflux with a 100-W lamp for 4 h.[12] After this time the mixture was cooled and filtered, and the solvent was removed to afford a yellow oil which solidified on cooling under 15 ml of anhydrous ether to give 1.0 g (72%) of crude **10**, mp 86–90 °C, the NMR spectrum of which showed no product of ring bromination, **9**. The solid was recrystallized twice from ether to give an analytical sample of **10**: mp 101–101.5 °C; NMR ($CDCl_3$) δ 7.30–7.60 (m, including s at 7.34, 7 H total), 6.17 (t, 1 H), 5.17 (s, 2 H), 4.47 (s, 2 H).

Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04. Found: C, 56.23; H, 4.43; N, 4.94.

The reaction was repeated using only 10 ml of carbon tetrachloride and the NMR of the crude solid showed the presence of 20–30% of **9**.

3-Bromomethyl-1-methyl-2-pyridone (6). In a dry nitrogen-filled 250-ml flask was placed a solution of 0.83 g (6.7 mmol) of **5** in 100 ml of dry carbon tetrachloride. To the solution was added 1.19 g (6.7 mmol) of purified NBS[9] and 0.15 g of dibenzoyl peroxide. The mixture was heated under reflux for 1 hr. After this time the mixture was cooled and filtered, and the solvent removed. The solid residue[10] was stirred under 10 ml of anhydrous ether and was removed by filtration to afford 0.85 g (63%) of **6** as tan crystals, mp 86–89 °C. The product was recrystallized twice from benzene to give an analytical sample of **6**: mp 101–101.5 °C (lit.[7] mp 98–99 °C); NMR ($CDCl_3$) δ 7.67 (m, 2 H), 6.31 (t, 1 H), 4.58 (s, 2 H), 3.65 (s, 3 H).

Anal. Calcd for C_7H_8BrNO: C, 41.61; H, 3.99; N, 6.93. Found: C, 41.68; H, 4.06; N, 6.83.

5-Bromo-1,3-dimethyl-2-pyridone (7). A solution of 0.83 g (6.7 mmol) of **5** in 12 ml of dry carbon tetrachloride was placed in a dry nitrogen-filled flask. To the solution was added 1.18 g (6.6 mmol) of purified NBS[9] and the mixture was heated under reflux for 30 min. After this time 25 ml of carbon tetrachloride was added; the mixture was cooled and filtered; and the solvent was removed to afford 1.28 g (96%) of **7** as a light-yellow solid,[11] mp 98–101 °C. Recrystallization of the product from petroleum ether (bp 30–60 °C) gave fluffy, white crystals: mp 105–106 °C (lit.[3] mp 106–107 °C); NMR ($CDCl_3$) δ 7.30–7.55 (m, 2 H), 3.61 (s, 3 H), 2.20 (s, 3 H).

Acknowledgment. The authors wish to express appreciation to the National Cancer Institute of the National Institutes of Health for partial support of this research by Grant CA 12149. One of the authors (D.L.C.) also expresses appreciation to the Graduate School of the University of New Hampshire for summer fellowships which provided partial support for this research.

Registry No.—**5**, 6456-92-4; **6**, 58802-10-1; **7**, 51417-13-1; **8**, 58802-11-2; **9**, 58802-12-3; **10**, 58802-13-4; 3-methyl-2-pyridone, 1003-56-1; benzyl chloride, 100-44-7; methyl iodide, 74-87-3; *N*-bromosuccinimide, 128-08-5.

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(9) The NBS was purified by recrystallization from ten times its weight of water and drying under vacuum overnight (mp 182.5–184 °C).
(10) The residue contained less than 10% of compounds **5** and **7**, combined, by NMR.
(11) The product contained only a trace (<2%) of compounds **5** and **6** by NMR.
(12) The manner and the time of heating after 50 min is not critical.

Biological Probes. 3. Methods for Carbon-4 and Carbon-5 Labeling in Nicotinamide

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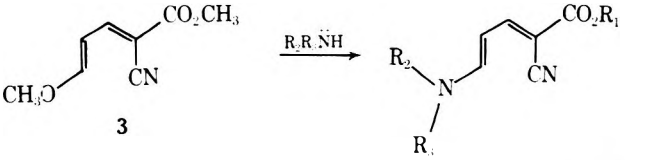
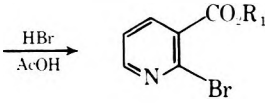
Increased interest in nonradioactive labels for use as general biological probes had led us to develop efficient methods for labeling the nicotinamide (**1**) portion of NAD^+ (**2**).[1-3] We have described facile pyridine syntheses in which nicotinamide can be labeled (^{13}C, ^2H, ^{15}N) at the 1, 2, 3, 6, and carbonyl positions and then be biosynthetically incorporated into the coenzyme NAD^+.[4] However, these methods were not useful for labeling the 4 position of the nicotinamide ring, the site at which biological oxidation–reduction occurs in NAD^+. We now wish to report an efficient, high-yield procedure for label incorporation (^{13}C, ^2H) at the 4 and also the 5 position of nicotinamide (**1**).

Prior experience with diene **3** as a labeled pyridine precursor suggested an attractive synthetic route to **1**. Our initial studies focused on modification of diene **3** with designs on making this general type of synthon more accessible from lower molecular weight, labeled starting materials. Specifically, diene **3** readily undergoes addition (1,6) of amines with loss of methanol forming butadienamines, such as **4**. These conjugated enamines (**4**), analogous to diene **3**, undergo acid-catalyzed (HBr/AcOH) cyclization to 2-bromonicotinate **5** in high yield.



3

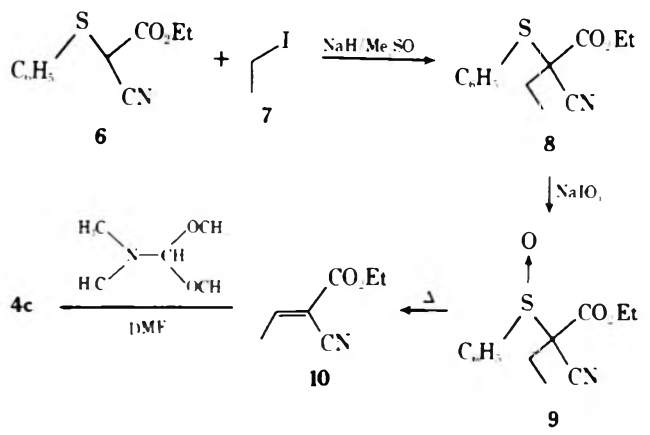
4a. $R_1 = R_2 = Me$; $R_3 = C_6H_5$
b. $R_1 = R_2 = R_3 = Me$
c. $R_1 = Et$; $R_2 = R_3 = Me$



5. R = Me or Et

Therefore, several routes to **3** or **4** were investigated with our labeling goals in mind resulting in the preparation of enamine **4c** as shown in Scheme I.

Scheme I



Sulfenyl cyanoacetate **6**, prepared by treating *N,N*-diethylbenzenesulfenamide[5] with cyanoacetate, can be alkylated using NaH in Me_2SO with specifically labeled ethyl iodide (**7**) affording the cyanobutyrate **8** in 84% yield. Using extended reaction times (48 h) and finely powdered $NaIO_4$,[7] cyanobutyrate **8** was smoothly oxidized to sulfoxide[8] **9** which was subjected in its crude form to thermolysis in refluxing toluene yielding ethylidene **10** in 89% yield. Transformation of **10** to enamine **4c** was achieved through an amide acetal condensation. Ethyl ethylidene cyanoacetate (**10**) when treated with *N,N*-dimethylformamide dimethyl acetal in warm DMF affords **4c** in 81% yield (60% from **6**). As cited above, **4c** undergoes facile HBr-catalyzed cyclization to 2-bromonicotinate **5** in 95% yield. Catalytic reduction of **5** followed by treatment with aqueous ammonia leads to nicotinamide (**1**, 45% yield from **6**) as described earlier.

Ethyl iodide was not our initial choice as a labeling unit. However, the reproducibly high yields obtainable from alkylation of **6** followed by subsequent formation of ethylidene **10** (75% from **6**) proved superior to alternatives such as a Knoevenagel condensation with cyanoacetate and acetaldehyde. Preliminary studies indicated that such reactions are at best low yield conversions to **10**, and the potential expense of using specifically labeled acetaldehyde is also prohibitive.

Through this and earlier studies, methods now exist for the preparation of specifically labeled nicotinamide from simple labeled precursors through convenient, high-yield reactions. In addition, such reactions would appear to be general and usable for the preparation of other important pyridine systems.[10]

Experimental Section[9]

Ethyl Phenylthiocyanoacetate (6)[6]. A mixture of *N,N*-diethylbenzenesulfenamide (24.54 g, 0.134 mol) and ethyl cyanoacetate (15.17 g, 0.134 mol) was stirred in methylene chloride (150 ml) at room temperature for 5 h. Removal of the volatiles at reduced pressure gave pale yellow crystals which were then stirred in a mixture of 10% hydrochloric acid (300 ml) and benzene (300 ml) at room temperature for 1 h. The benzene layer was separated and the solvent removed at reduced pressure to give 27.57 g of a pale yellow oil. Fractional distillation (120 °C, 2.5 mmHg) afforded 20.03 g (67%) of ethyl phenylthiocyanoacetate: ^1H NMR δ_{CDCl_3} (Me_4Si) 7.76–7.06 (m, 5 H, C_6H_5), 4.34 (s, 1 H, C_2 H), 4.16 (q, J = 7 Hz, 2 H, $-OCH_2$), 1.20 (t, J = 8 Hz, 3 H, $-CH_3$); ir (film) 2300, 1740, 1580 cm^{-1}; TLC (silica gel 1:1:1 $CH_3OH/EtOAc/CH_2Cl_2$) R_f 0.73; *m/e* 221.

Ethyl 2-Phenylthio-2-cyanobutyrate (8). Phenylthiocyanoacetate **6** (5 g, 22.7 mmol) was added to NaH (57% dispersion, washed once with hexane, 0.96 g, 1 molar equiv) in Me_2SO at 0 °C. The mixture was then allowed to equilibrate at room temperature for 20 min. Ethyl iodide (3.53 g, 22.7 mmol) was added and the mixture stirred for 6 h, diluted with H_2O (100 ml), and extracted with ether/hexane (3:1, 4 × 75 ml). The organic extracts were combined, washed with brine (100 ml), and dried (Na_2SO_4). Distillation (Kugelrohr oven, 0.5 mmHg, 120–135 °C) afforded 4.76 g (84%) of butyrate **8**: ir (film) 2250, 1740, 1580 cm^{-1}; ^1H NMR δ_{CDCl_3} (Me_4Si) 7.79–7.08 (m, 5 H, C_6H_5), 4.06 (q, 2 H, J = 7 Hz, $-OCH_2-$), 2.41–1.74 (m, 2 H, $-CH_2-$), 1.34–0.9 (m, 6 H, $-CH_3$); TLC (silica gel, $CHCl_3$) R_f 0.54; *m/e* 249. Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.64; H, 6.07. Found: C, 62.66; H, 6.02.

Ethyl 2-Cyano-2-butenoate (10). A saturated aqueous solution of finely powdered $NaIO_4$ (15 ml) was added to phenylthiocyanobutyrate **8** in MeOH (30 ml) at 0 °C. The mixture was stirred mechanically at 0 °C for 10 min and then at room temperature for 48 h. The mixture was diluted with H_2O (50 ml), extracted with $CHCl_3$ (4 × 75 ml), washed (NaCl), and dried ($MgSO_4$). The volatiles were removed at reduced pressure to afford 1.04 g of a yellow oil, which was dissolved in toluene (40 ml), stirred, and heated under reflux overnight. The mixture was concentrated at atmospheric pressure and distillation (Kugelrohr oven, 1.0 mmHg, 80 °C) afforded 0.45 g (89%) of butenoate **10**: ir (film) 2275, 1735, 1635 cm^{-1}; ^1H NMR δ_{CDCl_3} (Me_4Si) 7.78 (q, J = 8 Hz, 1 H, C_3 H), 4.38 (q, J = 7 Hz, 2 H, $-OCH_2$), 2.26 (d, J = 8 Hz, 3 H, $-C_4H_3$), 1.38 (t, J = 7 Hz, $-CH_3$); TLC (silica gel, $CHCl_3$) R_f 0.37 (0.54 starting material); *m/e* 139. Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52. Found: C, 60.39; 46.52.

Ethyl 5-(*N,N*-dimethylamino)-2-cyano-2,4-pentadienoate (4c). *N,N*-Dimethylformamide dimethyl acetal (0.31 g, 2.6 mmol) was added to ethyl 2-cyano-2-butenoate (0.35 g, 2.5 mmol) in DMF (1 ml). The mixture was stirred and heated at 75 °C for 5 h, cooled to room temperature, poured into benzene (20 ml), and washed with 1 N HCl (3 × 25 ml). The benzene solution was dried (Na_2SO_4) and the soluent removed at reduced pressure. Distillation (Kugelrohr oven, 140–150 °C, 2.5 mmHg) afforded 0.31 g (81%, mp 125–127 °C) of enamine **4c**: ir ($CHCl_3$) 2220, 1700, 1620, 1560 cm^{-1}; ^1H NMR δ_{CDCl_3} (Me_4Si) 7.78 (d, J = 13 Hz, 1 H, C_5 H), 7.10 (d, J = 13 Hz, 1 H, C_3H), 5.59 (t, J = 13 Hz, 1 H, C_4 H), 4.26 (q, J = 7 Hz, 2 H, $-OCH_2-$), 3.11 (s, 6 H, $-NCH_3$), 1.32 (t, J = 7 Hz, 3 H, $-CH_3$); λ_{max} (EtOH) 381 nm; TLC (silica gel, $CHCl_3$) R_f 0.08; *m/e* 194. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27. Found: C, 61.88; H, 7.25.

Ethyl 2-Bromonicotinate (5). Enamine **4c** (1 g, 3.49 mmol) was dissolved in 5 ml of acetic acid. An acetic acid solution of HBr (10 ml, saturated at 0 °C) was added dropwise to enamine **4c** while maintaining the reaction at 45 °C. After addition of the HBr solution, the temperature was raised to 55 °C and the mixture was allowed to stir for 2 h. The dark solution was cooled, poured into water, and neutralized by Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3 × 150 ml). The CH_2Cl_2 extracts were combined, washed once with H_2O (100 ml), and dried (Na_2SO_4). Evaporation of the volatiles at reduced pressure gave a dark oil. Distillation (Kugelrohr oven, 0.5 mmHg, 110–125 °C) afforded 0.76 g (95%) of ethyl 2-bromonicotinate: ^1H NMR δ_{CDCl_3} (Me_4Si) 8.47 (dd, $J_{6,4}$ = 2, $J_{6,5}$ = 5 Hz, 1 H, C_6H), 8.07 (dd, $J_{4,5}$ = 8.5, $J_{4,6}$ = 2 Hz, 1 H, C_4 H), 7.40 (dd, $J_{4,5}$ = 8.5, $J_{5,6}$ = 5 Hz, 1 H, C_5 H), 4.42 (q, J = 7 Hz, 2 H, $-OCH_2-$), 1.43 (t, J = 7 Hz, 3 H, $-CH_3$); ir ($CHCl_3$) 1735, 1580 cm^{-1}; TLC (silica gel, $CHCl_3$) R_f 0.24 (starting material, 0.08); *m/e* 230. Anal. Calcd for $C_8H_8NO_2Br$: C, 41.74; H, 3.51. Found: C, 41.70; H, 3.54.

Acknowledgment. We gratefully acknowledge the support of the National Cancer Institute of HEW (Grants CA17490 and CA15645) for support of this work.

Registry No.—**4c**, 51513-16-7; **5** (R = Et), 53087-78-8; **6**, 58734-93-3; **8**, 58734-94-4; **10**, 686-33-9; *N,N*-diethylbenzenesulfenamide, 6667-19-2; ethyl cyanoacetate, 105-56-6; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5.

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(8) Presence of sulfoxide [Ph–S(→O)–R] was detected by infrared absorption at 705 cm^{-1}.
(9) Structural assignments of all compounds are based on ir, ^1H NMR, uv, mass spectra, analysis and conversion to previously reported organic compounds.
(10) A variety of 2-substituted nicotinamide compounds exhibit anti-inflammatory activity.

Radical Additions to Alkenylidenecyclopropanes[1]

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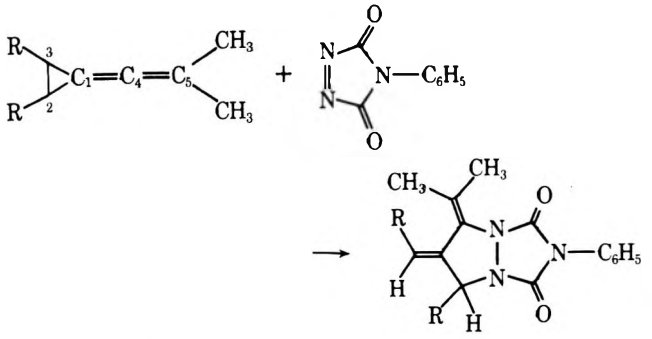
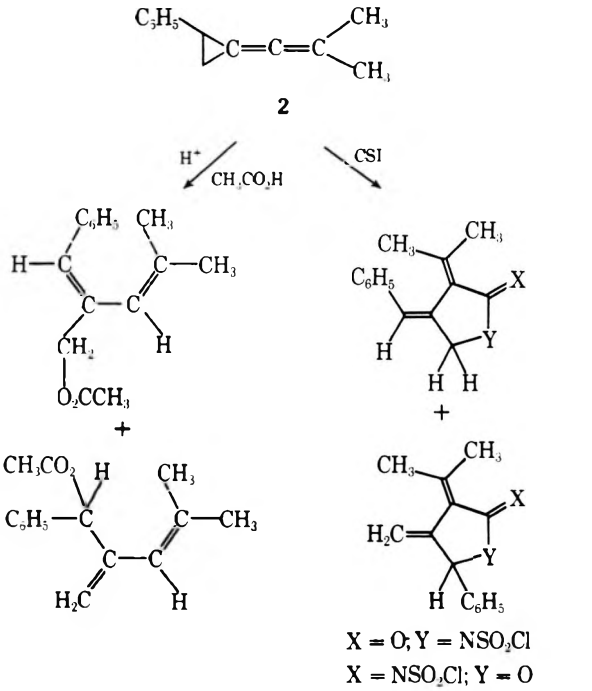
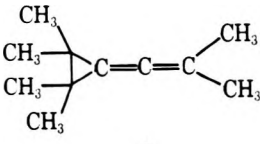
Recent studies in our laboratories have been directed toward gaining an understanding of the electronic structure of alkenylidenecyclopropanes and factors which determine reactivity and mode of reaction. Alkenylidenecyclopropanes (1) undergo cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) across the methylenecyclopropane portion of 1 regardless of the nature and number of groups attached to the three-membered ring.[2] Kinetic[3] and theoretical studies[4] have provided a detailed understanding of the bonding in 1



and of the mechanism of the cycloaddition reaction. In contrast to the uniform situselectivity exhibited in the cycloaddition reactions of 1 with PTAD, the site of attack by electrophilic reagents depends on the number and nature of the groups attached to the three-membered ring.[5] For example, the phenyl-substituted derivative 2 undergoes attack exclusively at the p orbital on C_4 of the C_1–C_4 double bond by electrophilic reagents such as proton and chlorosulfonyl isocyanate (CSI).[5] The incipient cyclopropyl cation undergoes ring opening subsequently producing substituted butadienes. The presence of a methyl group on the ring of 1 results in a predominant shift of electrophilic attack to C_5 (85%) to produce a β-lactam derivative, while with the tetramethyl derivative 3 electrophilic attack occurs exclusively at C_5.[5] In the



X = O; Y = NSO_2Cl
X = NSO_2Cl; Y = O



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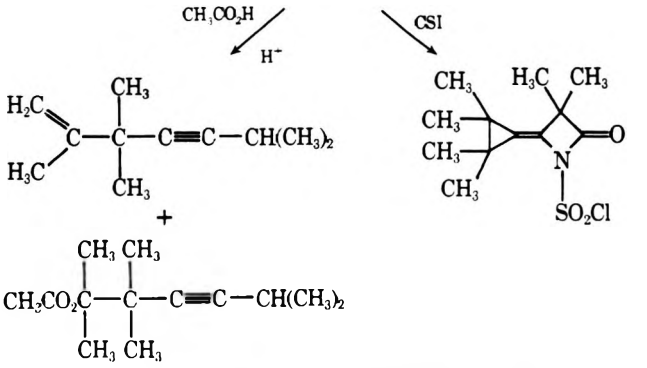
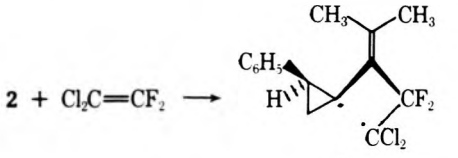


only study of the chemistry of alkenylidenecyclopropanes involving the formation of a radical intermediate 2 was found to react with 1,1-dichloro-2,2-difluoroethene to produce essentially only 5 via the diradical intermediate 4.[6] The present



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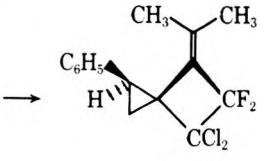
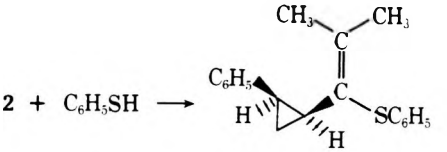


5

paper describes the course of reaction of substituted alkenylidenecyclopropanes in radical chain addition reactions with thiophenol.

Alkenylidenecyclopropanes **2**, **6**, and **3** rapidly react (15 min at 25 °C) with thiophenol either neat or in benzene solution open to the laboratory light and atmosphere. Measurement of the rates of reactions (by NMR) shows the presence of an induction period, and the addition of dissolved sulfur and freeze-degassing result in longer reaction times, all characteristic of typical free-radical chain addition reactions of thiophenol.[7] Also, the products formed in the reactions of **2**, **6**, and **3** with thiophenol do not possess structures typically derived in electrophilic additions to these substrates,[5] but are similar to that derived from 2 with 1,1-dichloro-2,2-difluoroethene.[6]

Thiophenol reacts with **2** to produce only **7**. The complexity of the NMR spectrum of **7** precluded assignment of the stereochemistry and stereochemical purity of the adduct. Ozonolysis of the product followed by basic hydrolysis gave pure (>98%) *cis*-2-phenylcyclopropanecarboxylic acid (**8**) demonstrating that **7** possesses the cis stereochemistry.



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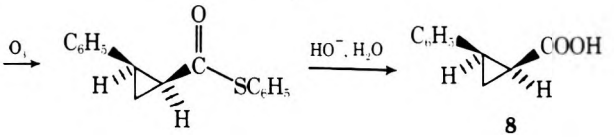
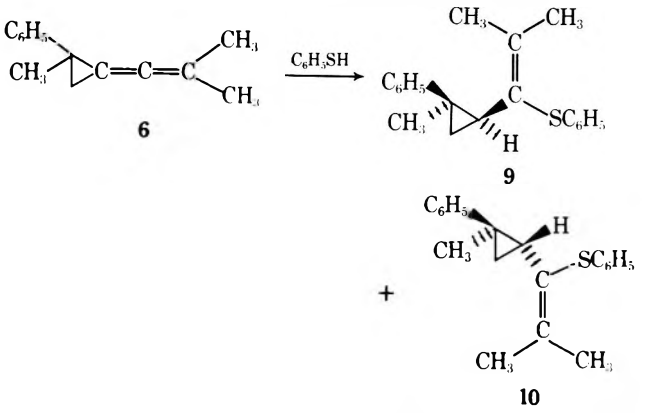


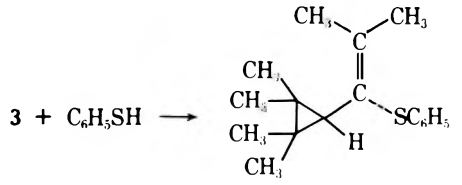
8

Reaction of **6** with thiophenol produces a mixture of **9** and **10** (65:35 ratio) which could not be separated. The stereochemistry of the two adducts is clearly indicated by the long-range shielding effects of the ring phenyl on the isopropylidene methyls, and of the thiophenyl group on the ring methyl.[8] In **9** the isopropylidene methyls appear at δ 1.84 and

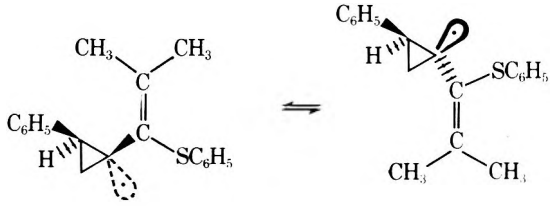


1.88, whereas in **10** they appear at δ 1.87 and 2.08. Similarly, the ring methyl of **9** appears at lower field (δ 1.47) than in **10** (δ 1.33). The ring hydrogens of the major isomer **9** are clearly evident as an ABX system, but those of **10** are obscured by the resonances of **9** and the methyl groups.

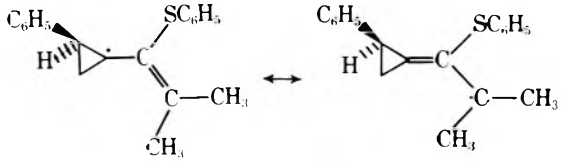
Reaction of **3** with thiophenol produces only **11**, which on ozonolysis produces 1 equiv of acetone.



In contrast to the different modes of reaction of **2**, **3**, and **6** with CSI, attack by thiophenoxy radical occurs at the same position to give products of similar structure. The structures of the products, however, do not indicate whether attack occurs on the C_1–C_4 double bond to initially produce radical **12**, or the C_4–C_5 double bond to give radical **13**, both of which are initially non-resonance-stabilized radicals. (Resonance stabilization of the radical centers in **12** and **13** requires an internal rotation of 90°, a process which may or may not be occurring simultaneously with attack by the thiophenoxy radical). Whether the radical center in the ultimate radical intermediate is nonplanar and non-resonance-stabilized, or is planar and resonance stabilized (i.e. **14**), is difficult to assess. Estimation of the relative energies of the two radicals leads to similar values. Addition to produce the nonplanar radical involves a reduction of ring strain from ~38.2 kcal/mol (42 kcal/mol ring strain for the methylenecyclopropane[9] minus the resonance energy of the alkenylidenecyclopropane system of 3.8 kcal/mol[4]) to ~27 kcal/mol (assumed to be the same as the ring strain of cyclopropane), a change of ~11.2 kcal/mol. Formation of the planar radical results in retention of the methylenecyclopropane ring strain and the resonance energy of the alkenylidenecyclopropane ring system, but yields an allyl radical possessing a resonance energy of ≥11.6 kcal/mol.[10] The stereochemistry of **7** is undoubtedly determined in the hydrogen atom abstraction step. Whether a rapidly inverting pair of nonplanar radicals[11] or a planar radical is involved, approach to the radical must occur highly preferentially at the face opposite the phenyl group on the ring thus producing **7**.



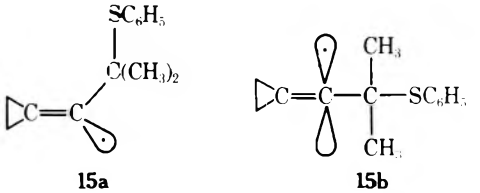
rapidly inverting, nonplanar radical



planar linear radical

In the radical derived from **6** the larger steric effect of the phenyl relative to the methyl group directs dominant hydrogen atom abstraction at the face opposite the phenyl to produce the major product **9**.

In view of the substantial directive effects exerted by alkyl groups attached to the three-membered ring on the position of electrophilic attack (i.e., exclusively at C_5 in **3**),[2,5] it is at first somewhat surprising that no radical attack occurs at C_5 of **3** to produce radical intermediate **15**. This would appear to be



due to the fact that vinyl cations prefer linear geometries[12] which would provide for excellent overlap of the vacant p orbital on C_4 with the orbitals of the three-membered ring,[4] whereas vinyl radicals prefer nonlinear geometries[13] (i.e., **15a**) in which overlap of the sp^2 hybrid orbital on C_4 with the orbitals of the three-membered ring would not be as favorable as in the linear radical **15b**.

Experimental Section

Reaction of 2 with Thiophenol. A solution of 500 mg (2.96 mmol) of **2** and 325 mg (2.96 mmol) of thiophenol in 10 ml of benzene was allowed to stand at 25 °C until no further reaction occurred as indicated by NMR analysis (0.5 h). The benzene solution was washed with 10% sodium hydroxide and water, and was dried ($MgSO_4$). The NMR spectrum of the residue obtained after removal of the solvent indicated the presence of **2** and **7**. A 200-mg portion of the residue was chromatographed on activity III alumina with hexane as eluent giving 17 mg of **2**, 24 mg of diphenyl disulfide (identified by its melting point

and NMR spectrum), and 116 mg of **7** as a pale yellow, viscous oil: NMR ($CDCl_3$) δ 1.25 (m, 2 H), 1.68 (bs, 3 H), 1.82 (d, J = 0.9 Hz, 3 H), 2.17 (m, 2 H), and 7.04 and 7.11 (s's, 5 H each); mass spectrum $M^{\cdot+}$ 280.1257, (calcd for $C_{19}H_{20}S$, 280.1254).

Conversion of 7 to *cis*-2-Phenylcyclopropanecarboxylic Acid (8). A solution of 80 mg of **7** in 2 ml of 1:1 dichloromethane–pyridine was cooled in a dry ice–acetone bath and was treated with a slight excess of ozone.[14] The reaction mixture was allowed to warm to 25 °C, poured into 25 ml of ether, and washed several times with 1 N hydrochloric acid. The extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure, giving a yellow, viscous oil (ir 1702 cm^{-1}).

The residue was dissolved in 10 ml of 10% sodium hydroxide in 50% aqueous ethanol. The mixture was refluxed for 40 min, cooled, poured into 20 ml of water, and extracted with ether. The aqueous layer was acidified with hydrochloric acid and was extracted with two 10-ml portions of ether. The ether extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure, leaving 15 mg of a tan solid whose NMR spectrum was identical with that of *cis*-2-phenylcyclopropanecarboxylic acid (8).[15] No peaks representing *trans*-2-phenylcyclopropanecarboxylic acid were present.

Reaction of 6 with Thiophenol. To a solution of 200 mg of **6** in 0.5 ml of hexadeuteriobenzene in an NMR tube was added 120 mg of thiophenol. The reaction mixture was thoroughly mixed and the rate of reaction was monitored with time by NMR. The reaction displayed an induction period of ~2 min, being essentially complete in 15 min at 39 °C. The resulting mixture was poured into 10 ml of ether and was extracted twice with 5-ml portions of 1 M sodium hydroxide, washed with water and saturated sodium chloride, and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was distilled in a microstill at 115 °C (0.07 mm), giving a pale yellow, viscous oil: NMR of **9** ($CDCl_3$) δ 0.88 (dd, J = 5.0 and 8.1 Hz), 1.08 (dd, J = 2.3 and 8.1 Hz), 1.47 (s), 1.63 (dd, J = 2.3 and 5.0 Hz), 1.84 and 1.88 (broadened s's), 7.18; **10**, δ 1.33 (s), 1.87 and 2.08 (broadened s's), 7.18 (the AMX double doublets are obscured by the more intense resonances of **9**); mass spectrum $M^{\cdot+}$ 294.1426 (calcd for $C_{20}H_{22}S$, 294.1442).

Reaction of 3 with Thiophenol. A solution of 430 mg (2.86 mmol) of **3** in 5 ml of benzene was added to 314 mg (2.86 mmol) of thiophenol dissolved in 5 ml of benzene. The reaction mixture was allowed to stand at room temperature for 3 h, at which time analysis by NMR indicated complete reaction. The benzene solution was washed with 15 ml of 10% sodium hydroxide and water, and was dried ($MgSO_4$). The benzene was removed under reduced pressure giving 656 mg of a pale yellow oil (**11**) bp ~50 °C (0.05 mm) in a molecular still; NMR ($CDCl_3$) δ 0.90 (s, 6 H), 0.98 (s, 6 H), 1.13 (m, 1 H), 1.83 (d, J = 1.6 Hz, 3 H), 1.92 (d, J = 2.2 Hz, 3 H), and 7.07 (m, 5 H); mass spectrum $M^{\cdot+}$ 260.1597 (calcd for $C_{17}H_{14}S$, 260.1608).

Ozonolysis of 11. A solution of 76 mg (0.30 mmol) of **11** in 1.75 ml of dichloromethane and 0.25 ml of pyridine[14] was cooled in a dry ice–acetone bath and ozone was bubbled through the solution for 15 s. The reaction mixture was allowed to warm to 25 °C and was analyzed directly by GLC on a Carbowax 20M column showing the presence of acetone by comparison of retention time with authentic material and admixture.

Registry No.—**2**, 4544-23-4; **3**, 13303,30-5; **6**, 40922-91-6; **7**, 58873-30-6; **8**, 939-89-9; **9**, 58873-31-7; **11**, 58873-32-8; thiophenol, 108-98-5.

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Trichloromethyl Chloroformate. Reaction with Amines, Amino Acids, and Amino Alcohols

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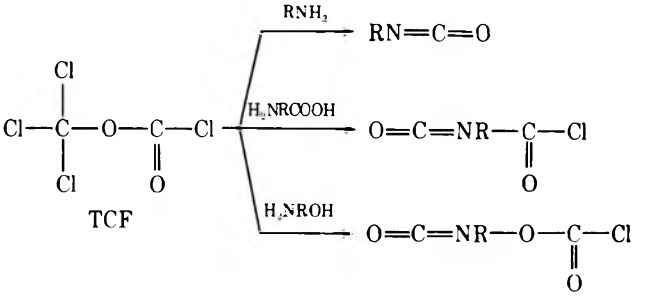
The title compound, trichloromethyl chloroformate (TCF), is of interest in that it is a potential substitute for phosgene, which presents a severe hazard in laboratory use because of its volatility and high toxicity. Although TCF is also toxic,[1] it is a dense liquid (bp 128 °C, d_{15}^{15} 1.65) with vapor pressure of only 10 mm at 20 °C. Thus TCF is more easily handled with safety, and seems to have significant advantages over phosgene.

Hentschel studied the decomposition of TCF and reactions with some organic compounds and found that phenyl isocyanate was formed by the action of TCF on 1,3-diphenylurea.[2] The reaction with alcohols to give carbonates has also been reported.[3] TCF was recently reported to be used as a substitute for phosgene in the preparation of *N*-carboxy-α-amino acid anhydrides; 1 mol of TCF provided the equivalent of 2 mol of phosgene in the NCA synthesis.[4]

To extend our knowledge of the reactivity of TCF, it was of interest to compare other reactions of TCF with those of phosgene. This paper describes the reaction of TCF with amines, amino acids, and amino alcohols to give the corresponding isocyanates, isocyanato acid chlorides, and isocyanato chloroformates.



The reactions of TCF with aniline were carried out under conditions similar to those employed in the phosgene method. As expected, phenyl isocyanate was obtained in high yields (78–89%) either from the hydrochloride or the free base. It was also confirmed that 0.5 mol of TCF was sufficient to convert 1 mol of the amine to the isocyanate.

Treatment of *p*-phenylenediamine hydrochloride with TCF in dioxane, on the other hand, gave only poor yields (23% or less) of the diisocyanate, even though the reaction was carried out under almost the same conditions used with phosgene. When the free base was used instead of the hydrochloride, the yield of the diisocyanate was improved to 47%. An attempted reaction of hexamethylenediamine hydrochloride with TCF in dioxane was unsuccessful and the hydrochloride was recovered. This result is presumably due to the high basicity of hexamethylenediamine compared to that of aromatic amines,

the more stable hydrochloride derived from the amine of higher basicity being less reactive to electrophilic attack.

The reactions of amino acids or amino alcohols with phosgene are interesting since they provide in one step molecules with two different functional groups, namely isocyanato acid chlorides or isocyanato chloroformates. The synthesis of 6-isocyanatohexanoyl chloride by the action of phosgene on the amino acid was reported to be attained only by using an additional reagent such as hydrogen chloride, thionyl chloride, or phosphorus pentachloride besides phosgene.[5] When TCF was used in this preparation, however, 6-isocyanatohexanoyl chloride was obtained in 73% yield without an additional reagent. TCF also reacted smoothly with 3-aminopropanoic acid, and in contrast to phosgene, 3-isocyanatopropanoyl chloride was obtained quantitatively (97%).

In contrast to the preparation of alkyl isocyanato acid chlorides, the TCF method with aromatic amino acids gave results similar to those with phosgene.[5] Treatment of *o*-aminobenzoic acid with TCF resulted in the formation of isatoic anhydride in a quantitative yield, as observed with phosgene. The reaction between *m*-aminobenzoic acid and TCF failed to give the corresponding isocyanato acid chloride, and only an unidentified white solid was obtained. It was confirmed that an additional reagent such as phosphorus pentachloride was necessary to prepare *o*-isocyanatobenzoyl chloride (85% yield) as in the phosgene method.[5]

Reactions of amino alcohols with TCF proceeded similarly to those with phosgene.[6] 3-Aminopropanol and 2-aminoethanol gave 3-isocyanatopropyl chloroformate and 2-isocyanatoethyl chloroformate, respectively, in 53 and 21% yields.

Thus it was found that TCF is far superior to phosgene in the alkyl isocyanato acid chlorides syntheses, but was comparable to phosgene in the preparations of phenyl isocyanate, aromatic isocyanato acid chlorides, and alkyl isocyanato chloroformates.

Experimental Section[7]

Phenyl Isocyanate. To a mixture of 12.95 g (0.1 mol) of aniline hydrochloride and 100 ml of dry dioxane was added 6.3 ml (10.4 g, 0.05 mol) of TCF. The mixture was heated at 60 °C; after 1.5 h of stirring, it became a clear solution. Heating was discontinued after 3.5 h and the solvent was removed under reduced pressure. The residue was distilled at 70–73.5 °C (36 mm) to give 10.6 g (89%) of phenyl isocyanate. It was redistilled almost quantitatively, bp 75–77 °C (39 mm) [lit.[8] 55–57 °C (16 mm)].

***p*-Phenylene Diisocyanate. A. From the Hydrochloride.** To 100 ml of dry dioxane were added 14.48 g (0.08 mol) of *p*-phenylenediamine hydrochloride and 51 ml (84.2 g, 0.4 mol) of TCF. The mixture was heated at reflux for 20 h. The unreacted hydrochloride was filtered off and the filtrate was evaporated under reduced pressure. The residual white, crystalline solid was sublimed under vacuum to give 3.0 g (23%) of *p*-phenylene diisocyanate. It was sublimed again at 85 °C (7 mm) to give colorless crystals, mp 92–94 °C (lit.[8] 94–96 °C).

B. From the Free Base. To a solution of 8.64 g (0.08 mol) of *p*-phenylenediamine in 100 ml of dry dioxane was added 20.5 ml (34.8 g, 0.16 mol) of TCF with stirring. Precipitation took place instantaneously. After refluxing the mixture for 20 h, the undissolved white solid was filtered off and the filtrate was evaporated. The residual solid gave 6.0 g (47%) of *p*-phenylene diisocyanate on sublimation.

3-Isocyanatopropanoyl Chloride. To 250 ml of dry dioxane were added 12.6 g (0.1 mol) of powdered 3-aminopropanoic acid hydrochloride and then 37.9 ml (62.6 g, 0.3 mol) of TCF with stirring. The mixture became a clear solution after heating at 55 °C for 4.5 h. The heating was continued for an additional 6.5 h and then the solvent was removed under reduced pressure. The residual oil was distilled to give 13.0 g (97%) of 3-isocyanatopropanoyl chloride, bp 77–80 °C (10 mm) [lit.[5] 91–91.5 °C (24.5 mm)].

6-Isocyanatohexanoyl chloride was synthesized by virtually the same procedure, bp 112–113 °C (5 mm) [lit.[5] 114 °C (6 mm)].

Reaction of *o*-Aminobenzoic Acid with TCF. A. Without PCl_5. A mixture of 10.0 g (0.073 mol) of *o*-aminobenzoic acid and 36.8 ml (60.7 g, 0.3 mol) of TCF in 150 ml of dry dioxane was refluxed for 6 h. The resulting clear solution was evaporated to give a white solid. It was recrystallized from tetrahydrofuran to give 10.0 g (92%) of isatoic anhydride, mp 241–243 °C dec (lit.[5] 242–243 °C dec).

B. With PCl_5. To a mixture of 10.0 g of o-aminobenzoic acid and 36.8 ml of TCF in 150 ml of dry dioxane was added 15.2 g (0.073 mol) of phosphorus pentachloride with stirring. Phosphorus pentachloride went into solution in 1 h. The solution was allowed to stand at room temperature overnight and then the solvent was removed under reduced pressure. The residue was distilled two times to give 11.2 g (85%) of *o*-isocyanatobenzoyl chloride, bp 108–109.5 °C (2 mm), mp 30–32 °C (lit.[5] 32 °C).

3-Isocyanatopropyl Chloroformate. To a solution of 48.4 ml (79.8 g, 0.4 mol) of TCF in 250 ml of dry dioxane was added 7.5 g (0.1 mol) of 3-aminopropanol dropwise over a period of 1 h with cooling in an ice bath. The mixture was stirred with cooling for 30 min and then left standing at room temperature overnight. The solution was evaporated under reduced pressure and the residue was distilled to give 10.2 g of distillate boiling at 65–105 °C (7 mm). Fractional redistillation afforded 0.5 g of a forerun boiling at 23–60 °C (1 mm) and 8.7 g (53%) of 3-isocyanatopropyl chloroformate boiling at 70–74.5 °C (1 mm) [lit.[6] 82 °C (1.5 mm)]. The forerun was considered to consist of mostly 3-chloropropyl isocyanate from its boiling range [lit.[6] 34 °C (1.5 mm)] and ir spectrum.

2-Isocyanatoethyl Chloroformate. 2-Aminoethanol (6.1 g, 0.1 mol) was treated with 24.2 ml (40 g, 0.2 mol) of TCF in 250 ml of dry dioxane at 55–60 °C for 6 h. Fractional distillation gave 0.7 g (3%) of 2-chloroethyl isocyanate boiling at 41.5–45 °C (13 mm) [lit.[6] 35–36 °C (13 mm)], 3.2 g (21%) of 2-isocyanatoethyl chloroformate boiling at 89.5–90 °C (14 mm) [lit.[6] 86–87 °C (13 mm)], and 1 g (6%) of 2-oxazolidone boiling at 160–165 °C (2 mm), mp 86–88 °C (lit.[6] 89 °C).

Acknowledgment. The authors wish to express their appreciation to Hodogaya Kagaku Kogyo Co. for a gift of TCF.

Registry No.—Phenyl isocyanate, 103-71-9; aniline hydrochloride, 142-04-1; *p*-phenylene diisocyanate, 104-49-4; *p*-phenylenediamine hydrochloride, 624-18-0; *p*-phenylenediamine, 106-50-3; 3-isocyanatopropanoyl chloride, 3729-19-9; 3-aminopropanoic acid hydrochloride, 6057-90-5; 6-isocyanatohexanoyl chloride, 3729-18-8; *o*-aminobenzoic acid, 118-92-3; isatoic anhydride, 118-48-9; *o*-isocyanatobenzoyl chloride, 5100-23-2; 3-aminopropanol, 156-87-6; 3-isocyanatopropyl chloroformate, 13107-90-9; 3-chloropropyl isocyanate, 13010-19-0; 2-aminoethanol, 141-43-5; 2-chloroethyl isocyanate, 1943-83-5; 2-isocyanatoethyl chloroformate, 13107-89-6; 2-oxazolidone, 497-25-6; TCF, 23213-83-4; PCl_5, 10026-13-8.

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An Electron Spin Resonance Study of the Radical Anion of 7,8-Dimethylene-1,3,5-cyclooctatriene

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Received February 20, 1976

Several examples of pericyclic reactions in radical anions are known where the stereochemistry is the same as that of the excited state of the neutral molecule.[1] If these reactions are concerted, the parallel mode of reaction of the radical anions with the excited states is predicted by the highest occupied molecular orbital (HOMO) method.[2] Bauld and Cessac[3] have recently noted that the butadiene–cyclobutene

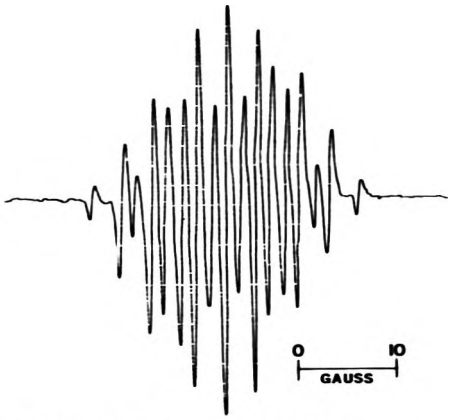
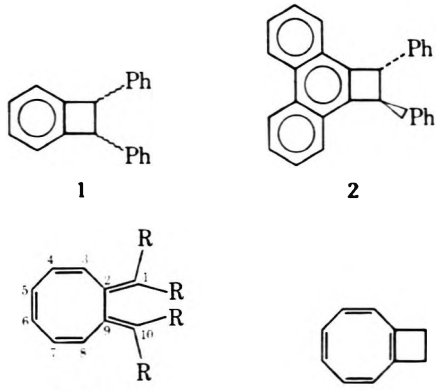


Figure 1. ESR spectrum of **3a**·⁻ in DMF at −60 °C.

radical anion transformation is allowed in the disrotatory mode by the HOMO method but is not allowed in either the disrotatory or conrotatory mode hy the orbital correlation diagram (OCD) method.[4] INDO/MO calculations were carried out on this transformation giving a considerably lower barrier for the conrotatory mode. Interestingly, the radical anions of *cis*- and *trans*-**1**[5] and **2**[3] were found to undergo the cyclobutene to butadiene radical anion type transformation primarily in the conrotatory mode. We wish to report our preparation of the radical anion of 7,8-dimethylene-1,3,5-cyclooctatriene (**3a**) and our observation that this type of transformation does not take place between **3a**·⁻ and **4**·⁻ in either direction.



Using special precautions to prevent exposure to oxygen,[6] a solution of **3a**[7] in deoxygenated DMF containing *n*-Bu_4NClO_4 was introduced into a standard variable temperature electrolytic cell. Reduction of this solution at −60 °C in an ESR cavity produced the spectrum shown in Figure 1 which could be satisfactorily simulated with a^H = 4.31 (2 H) and 3.10 G (6 H). Although the signal intensity decreased considerably upon warming to 0 °C, no evidence for a second radical could be found. Electroreduction of **3b** at −60 °C gave an ESR spectrum with a^H = 4.31 (2 H) and 3.43 G (2 H) and a small hyperfine splitting (hfs) of 0.44 G presumably for four deuteriums. An excellent simulation of the spectrum in Figure 1 was then obtained using a^H = 4.31 (2 H), 3.43 (2 H), and 2.96 G (4 H) with a line width of 0.50 G.

The above results support our assignment of structure **3a**·⁻ to the radical anion obtained from electroreduction of **3a** where the methylene hydrogens have a hfs of 2.96 G. Further support for this assignment comes from HMO and McLachlan[8] calculations carried out on **3a**·⁻ assuming a planar geometry. In Table I are given Hückel and McLachlan spin densities (p_c) along with those calculated from hfs's using the McConnell equation,[9] $a^H = -24p_c$. Excellent agreement is obtained suggesting that **3a**·⁻ is planar or very nearly so. The very small McLachlan spin densities at C-4 and C-7 nicely explain why only eight of the ten hydrogens in **3a**·⁻ give observable hfs's.

Table I. Spin Densities for 3a·⁻

Position	Hückel	McLachlan	Exptl
1,10	0.1236	0.1767	0.1233
2,9	0.0120	−0.0353	
3,8	0.1822	0.2361	0.1796[a]
4,7	0.0586	0.0037	
5,6	0.1236	0.1188	0.1429[a]

[a] Assignment made based on the MO calculations.

Bauld and co-workers have reduced **4** electrochemically (presumably at room temperature) and have obtained an ESR spectrum with a^H = 5.40 (4 H) and 3.25 G (6 H).[10] Although assignment of this radical anion to structure **4**·⁻ is reasonable

4·⁻ **5**·⁻

in view of the hfs of 3.21 G for the hydrogens in the cyclooctatetraene radical anion, we decided to prepare the radical anion of 1,2-dimethylcyclooctatetraene (**5**) for comparison. Reduction of **5** with a solution of Na in HMPA gave an ESR spectrum with hfs's of 3.38 (6 H) and 2.75 G (6 H) while reduction electrolytically in DMF (*n*-Bu_4NClO_4 as supporting electrolyte) at −65 °C gave a^H = 3.49 (6 H), 2.95 (4 H), and 2.62 G (2 H). The similarity in hfs's between **4**·⁻ and **5**·⁻ certainly confirms their assignment. The methylene splitting of 5.40 G in **4**·⁻ is 60% greater than the methyl splitting of 3.38 G in **5**·⁻ (HMPA) largely as a result of a conformational effect.[10]

A state correlation diagram for **3a**·⁻ (using Hückel energy levels) and **4**·⁻ reveals that transformation between ground states is allowed in the conrotatory mode if the degeneracy of ψ_4 and ψ_5 in **4**·⁻ is removed by placing the symmetric (C_2 axis) orbital higher in energy. Our results clearly show that the transformation of **3a**·⁻ to **4**·⁻ does not take place thermally under the conditions given. Since the width of the ESR spectrum for **4**·⁻ (41.1 G) is considerably greater than that for **3a**·⁻ (27.3 G), even a trace of **4**·⁻ would have been detected. The reverse reaction can also be ruled out based on earlier work.[10] We are presently investigating whether phenyl substituents at the methylene positions of **4**·⁻ will significantly reduce the energy barrier between **4**·⁻ and **3a**·⁻

Experimental Section

General. The ESR spectra were recorded on a Varian Associates V-4502 spectrometer. Electroreductions were carried out at a mercury surface using DMF which was previously distilled from CaH_2. HMPA was distilled from sodium prior to use as a solvent for sodium reductions.

Electroreduction of 3a. 7,8-Dimethylene-1,3,5-cyclooctatriene (**3a**) was prepared by the literature method[7] and immediately purified before use by chromatography on silica gel and elution with deoxygenated pentane under N_2. The bulk of the pentane was removed below room temperature by passing a stream of N_2 through the solution. Deoxygenated DMF was then added before the remainder of the pentane was removed by the same procedure. Addition of the electrolyte, tetra-*n*-butylammonium perchlorate, and transfer to the electrolytic cell was also carried out under N_2.

Preparation of 3b. Using the literature methods for preparing **3a**,[7,11,12] **3b** was synthesized from 1,2-dicarbomethoxycyclooctatetraene and aluminum deuteride: NMR (CCl_4) δ 5.67–6.00 (m, 4) and 6.16–6.42 (m, 2).

1,2-Dimethylcyclooctatetraene was prepared by the literature method.[13]

Acknowledgment. The authors are grateful to the Research Corporation for financial support. We wish to thank Professor Glen A. Russell for carrying out the MO calculation on $3a\cdot^-$.

Registry No.—**3a**, 10474-58-4; $3a\cdot^-$, 58873-29-3.

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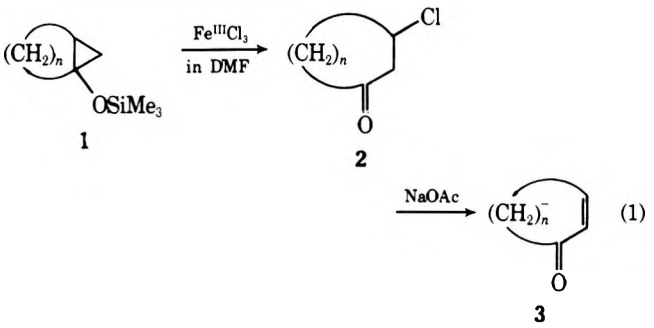
Communications

Reaction of 1-Silyloxybicyclo[*n*.1.0]alkanes with $Fe^{III}Cl_3$. A Facile Synthesis of 2-Cycloalkenones via Ring Enlargement of Cyclic Ketones

Summary: Reactions of 1-trimethylsilyloxybicyclo[*n*.1.0]-alkanes (**1**) with $Fe^{III}Cl_3$, followed by treatment with sodium acetate in methanol, furnish 2-cycloalkenones (**3**) in high yields; similar reactions with bis(trimethylsilyloxy)bicyclo[*n*.1.0]alkanes (**4**) afford cycloalkane-1,3-dione (**5**) in moderate yields.

Sir: Much attention has been directed to the utilization of silyl groups in organic synthesis in the past several years.[1] In our previous paper,[2] we described a regiospecific formation of 1,4 diketones by the oxidative coupling of silyl enol ethers with Ag_2O, in which we assumed Ag^I enolate intermediate regiospecifically formed through the reaction of silyl enol ether with Ag_2O. Herein, we wish to report an oxidation reaction of 1-silyloxybicyclo[*n*.1.0]alkanes (**1**) with $Fe^{III}Cl_3$, leading to the formation of the corresponding 2-cycloalkenone (**3**) via 3-chlorocycloalkanone (**2**) in moderate to excellent yields according to the eq 1. This reaction presents a new method for



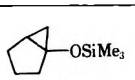
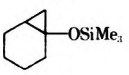
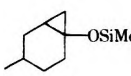
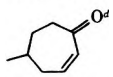
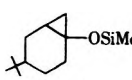
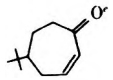
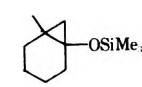
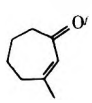
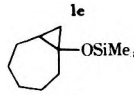
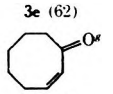
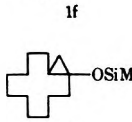
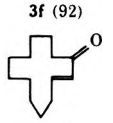
1 2 3 (1)

one-carbon ring homologation of cycloalkanones. It is of practical use since 1-silyloxybicyclo[*n*.1.0]alkanes are readily prepared by the Simmons–Smith reaction of silyl enol ethers of cycloalkanones.[3] Recently, Stork has reported a comparable ring homologation of cycloalkanones by the dichlorocyclopropanation of silyl enol ether followed by hydrolysis.[4]

A typical experimental procedure is illustrated by the reaction of 1-trimethylsilyloxybicyclo[4.1.0]heptane (**1b**) with $Fe^{III}Cl_3$. To a stirred solution of anhydrous $Fe^{III}Cl_3$ (973 mg, 6 mmol) in dimethylformamide (4 ml), a solution of **1b** (368 mg, 2 mmol) and pyridine (158 mg, 2 mmol) in dimethylformamide (4 ml) was added dropwise over 2 h at 0 ~ 10 °C under nitrogen. The resultant brown solution was stirred at room temperature for 1 h, and then poured into cold 1 N HCl aqueous solution and extracted repeatedly with chloroform. The chloroform extract was successively washed with 1 N HCl aqueous solution and with brine, dried over $MgSO_4$ and concentrated in vacuo. The concentrate was subjected to preparative GLC to afford 3-chlorocycloheptanone (**2b**) in 93% yield: ir 1705 cm^{-1}; NMR (CCl_4 with TMS) δ 1.4 ~ 2.3 (m, 6 H), 2.3 ~ 2.6 (m, 4 H), 4.1 ~ 4.4 (m, 1 H); mass M^+ 146 and 148 (3:1). After the concentrate was refluxed with sodium acetate in methanol for 2 h, 2-cycloheptenone (**3b**) was isolated in 84% yield by preparative GLC, which was identical in all respects with an authentic sample. No C_7 cyclic ketones other than **3b** were detected in the reaction mixture by GLC. Some results of 2-cycloalkenone synthesis are summarized in Table I.

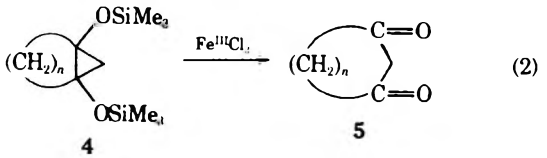
Some remarks are to be added to Table I. The reaction of 1-trimethylsilyloxybicyclo[3.1.0]hexane (**1a**) with $Fe^{III}Cl_3$ at 0 ~ 10 °C produced 2-cyclohexenone (**3a**)[5] in almost quantitative yield prior to the treatment with sodium acetate in methanol. In this case, 3-chlorocyclohexanone (**2a**) initially formed underwent readily dehydrochlorination under the reaction conditions. The reaction with 1-trimethylsilyloxy-6-methylbicyclo[4.1.0]heptane (**1e**) afforded 3-methyl-2-cycloheptenone (62% isolated yield), after the treatment with sodium acetate, which was not contaminated with any isomeric methylcycloheptenones. This reaction represents a transformation of unsymmetrical cycloalkanone into regiospecifically homologated 2-cycloalkenone. The reaction of 1-trimethylsilyloxybicyclo[10.1.0]tridecane (**1g**) with $Fe^{III}Cl_3$, which was very sluggish at 0 ~ 10 °C, was carried out by heating at 80 °C for 3 h. Oxidative cleavage of the carbon–carbon bond of **1g** and dehydrochlorination of the resulting 3-chlorotridecanone (**2g**) took place successively in one flask at a temperature of 80 °C.[6] The product of *trans*-2-cyclotridecenone (**3g**) was isolated in 81% yield by preparative TLC on silica gel: ir 1690, 1662, 1625 cm^{-1}; NMR (CCl_4 with TMS) δ 1.15 ~ 1.85 (m, 16 H), 2.10 ~ 2.50 (m, 4 H), 6.05 (d, 1 H, J = 15.6 Hz), 6.61 (td, 1 H, J = 15.6 and 7.0 Hz); mass M^+ 194. Use of diethyl ether solvent[7] in the ring enlargement reaction resulted in a remarkable reduction in the yield of the corresponding 2-cycloalkenone [e.g., 5-methyl-2-cycloheptenone (47%), *trans*-2-cyclotridecenone (56%)]. $CuCl_2$ can also be used in place of $Fe^{III}Cl_3$ in the present reaction, but was less effective [e.g., 2-cyclohexenone (60% yield)] than $Fe^{III}Cl_3$.

Table I. Synthesis of 2-Cycloalkenone

No.	1-Silyloxybicyclo-[n.1.0]alkane	2-Cycloalkenone[a] (yield, %)[b]
1	 1a	 3a (98)
2	 1b	 3b (84)
3	 1c	 3c (97)
4	 1d	 3d (70)
5	 1e	 3e (62)
6	 1f	 3f (92)
7	 1g	 3g (81)

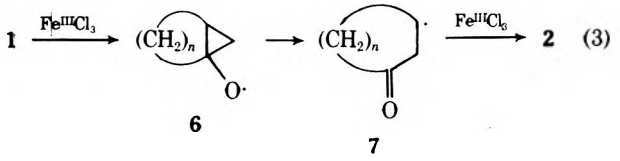
[a] Satisfactory microanalysis data were obtained for all new compounds. [b] No attempt has been made to optimize the reaction conditions. [c] Cis–trans mixture, as judged by NMR. [d] An axial–equatorial mixture. **3c**: ir 1665 cm^{-1}; NMR (CCl_4, with TMS) δ 1.05 and 1.08 (two d, 3 H, J = 6.0 Hz), 1.5~2.1 (m, 3 H), 2.1~2.5[4] (m, 4 H), 5.84 (br d, 1 H, J = 12.0 Hz), 6.40 (m, 1 H). [e] An axial–equatorial mixture. **3d**: ir 1665 cm^{-1}; NMR (CCl_4 with TMS) δ 0.90 and 0.95 (two s, 9 H), 1.2~2.6 (m, 7 H), 5.80 (br d, 1 H, J = 12.0 Hz), 6.43 (m, 1 H). [f] **3e**: ir 1650 cm^{-1}; NMR (CCl_4 with TMS) δ 1.97 (s, 3 H), 1.7~2.0 (m, 4 H), 2.3~2.7 (m, 4 H), 5.85 (broad s, 1 H). [g] **3f**: ir 1660 cm^{-1}; NMR (CCl_4 with TMS) δ 1.4~2.2 (m, 6 H), 2.3~2.7 (m, 4 H), 5.81 (d, 1 H, J = 12.0 Hz), 6.14 (td, 1 H, J = 12.0 and 6.0 Hz).

The present procedure for one-carbon ring homologation of cyclic ketone is also applicable to bis(trimethylsilyloxy)-bicyclo[n.1.0]alkanes (**4**) which are prepared by the cyclopropanation of bis(silyloxy)enediol derived from the silyl-acyloin synthesis.[8] This reaction provides a new route to cycloalkane-1,3-diones (**5**, eq 2) [e.g., cycloheptane-1,3-dione (68%), cyclonane-1,3-dione (72% yield)].



4 **5** (2)

The reaction for one-carbon homologation of cycloalkanones in this study is mechanistically interesting in terms of the regioselectivity in the ring-opening of silyloxybicyclo[n.1.0]alkane (**1** and **4**), of which the bridging bond is cleaved. This is contrasted with the bromination[9] and the potassium *tert*-butoxide treatment[10] of 1-silyloxybicyclo[n.1.0]alkanes producing 2-bromomethylcycloalkanones and 2-methylcycloalkanones, respectively. Based upon the extensive studies on the reaction of cyclopropanol with various halogenating reagents by DePuy and coworkers,[7] the present ring enlargement reaction may be well explained by a mechanism involving an alkoxy radical intermediate (**6**) which undergoes the homolytic β scission of the bridging carbon–carbon bond, and the subsequent abstraction of chlorine by the resulting carbon radical species (**7**) to give 3-chlorocycloalkanone (**2**) (eq 3). Detailed understanding of the reaction mechanism must await further study.



6 **7** (3)

Ring enlargement of the related silyloxybicycloalkanes is now being carried out in this laboratory.

Acknowledgment. We are grateful to Shinetsu Chemical Industry Co., Ltd., for providing the trimethylsilyl chloride.

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(5) Identical in all respects with an authentic sample.
(6) The 2-cycloalkenone synthesis in this study can be also performed in one flask by heating the reaction mixture of **1**, pyridine, and $Fe^{III}Cl_3$ in DMF at 80 °C, but in decreased yields [for example, 5-methyl-2-cycloheptenone (**3c**) (65% yield)].
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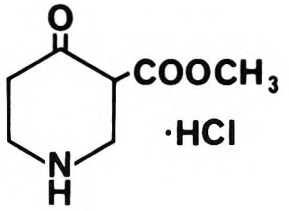
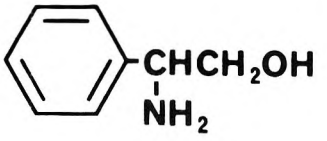
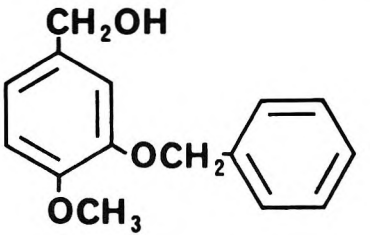


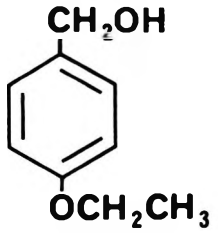
19,151-5
Methyl 4-oxo-3-piperidinecarboxylate hydrochloride
5g $12.75 25g $42.50



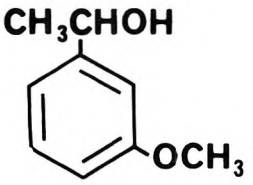
19,035-7
D-(-)-α-Phenylglycinol
5g $9.00 25g $30.00



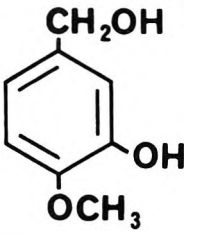
18,899-9
3-Benzyloxy-4-methoxybenzyl alcohol
5g $6.10 25g $23.50



19,047-0
***p*-Ethoxybenzyl alcohol**
10g $6.75 50g $22.00

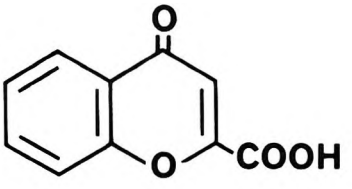


19,036-5
***m*-Methoxy-α-methylbenzyl alcohol**
10g $9.80 50g $34.00

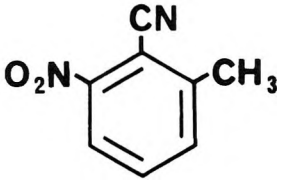


18,843-3
3-Hydroxy-4-methoxybenzyl alcohol
10g $5.80 50g $18.00

19,146-9
Cyclohexanone cyanohydrin
25g $7.50 100g $20.00



18,978-2
4-Oxo-4H-1-benzopyran-2-carboxylic acid
5g $5.00 25g $10.50



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